VOLUME 1 • NOVEMBER 1959 • NUMBER 5

A.M.A. ARCHIVES OF NEUROLOGY

"What Is Past Is Prologue"
Byron Stookey

Familial Periodic Paralysis
Raymond F. Chen

Spinal Cord Convulsions
Don W. Esplin

Carotid Artery Occlusive Syndrome
L. J. Hurwitz, Sigmund N. Groch, Irving S. Wright, and Fletcher H. McDowell

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Some Properties of Brain Copper-Proteins in Hepatolenticular Degeneration
Huntington Porter

Augmentation of the Inflammatory Reaction by Activity of the Central Nervous System
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Archives of Neurology

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Their Plasma Concentration in Hypertension, Shock, and Mental Disease, With Some Metabolic Studies

By
WILLIAM MUIR MANGER, B.S., M.D., Ph.D.
Department of Medicine
College of Physicians and Surgeons
New York City, New York
Formerly, Fellow in Medicine
Mayo Foundation
Rochester, Minnesota

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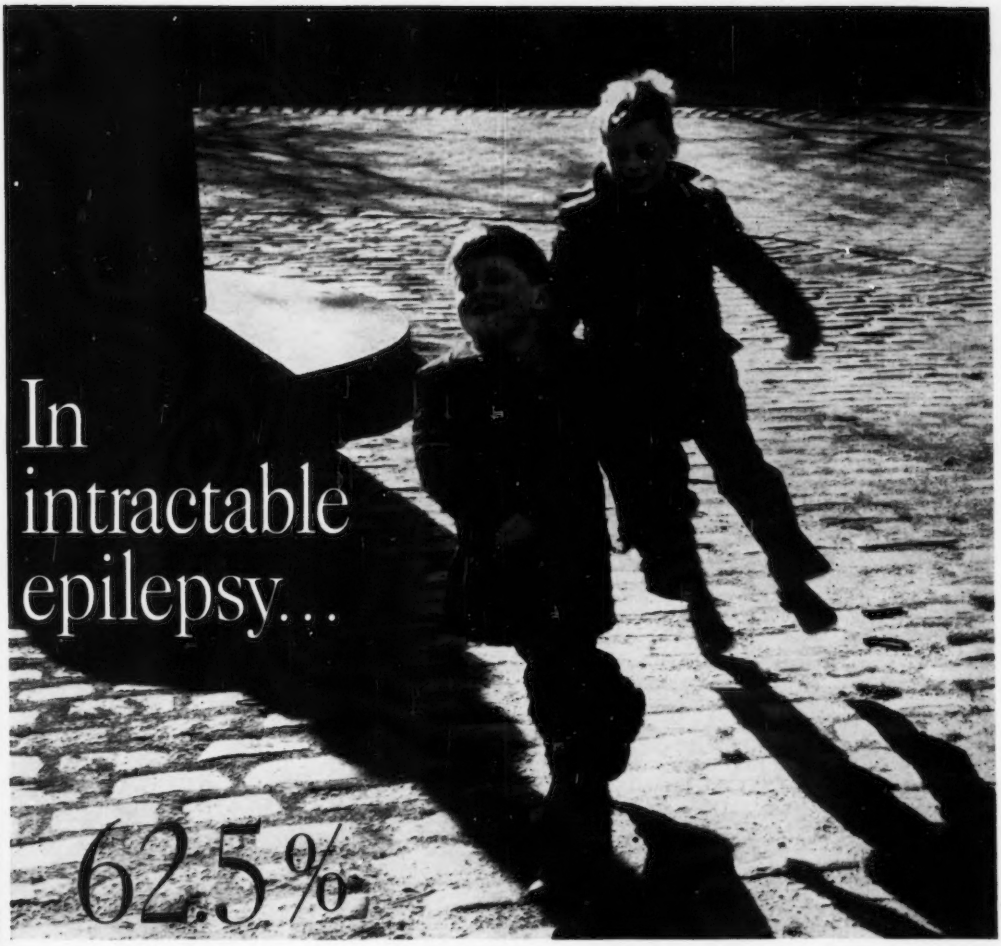

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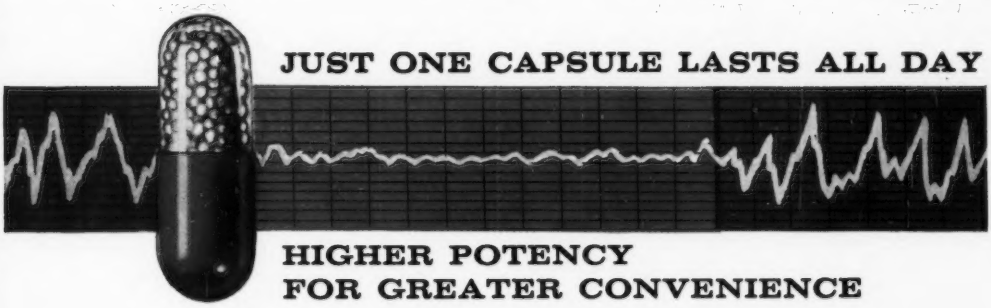

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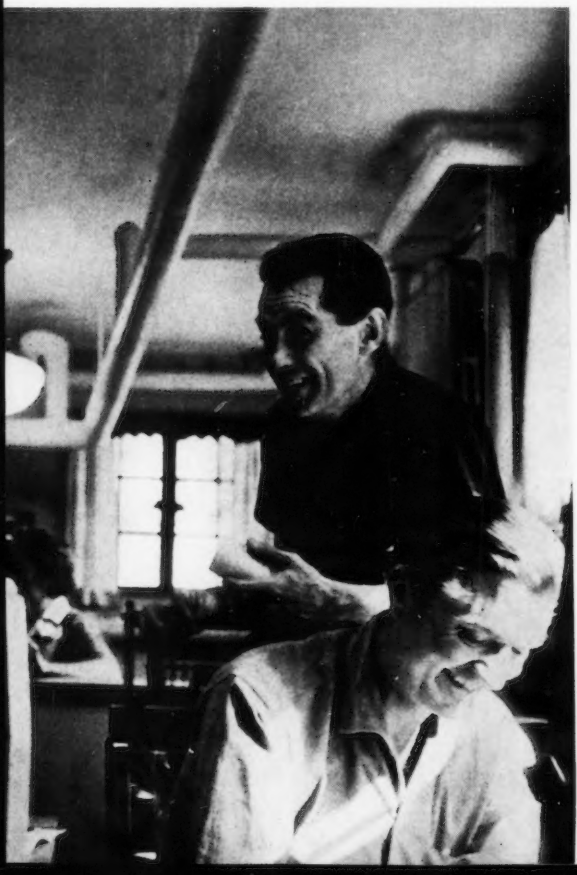

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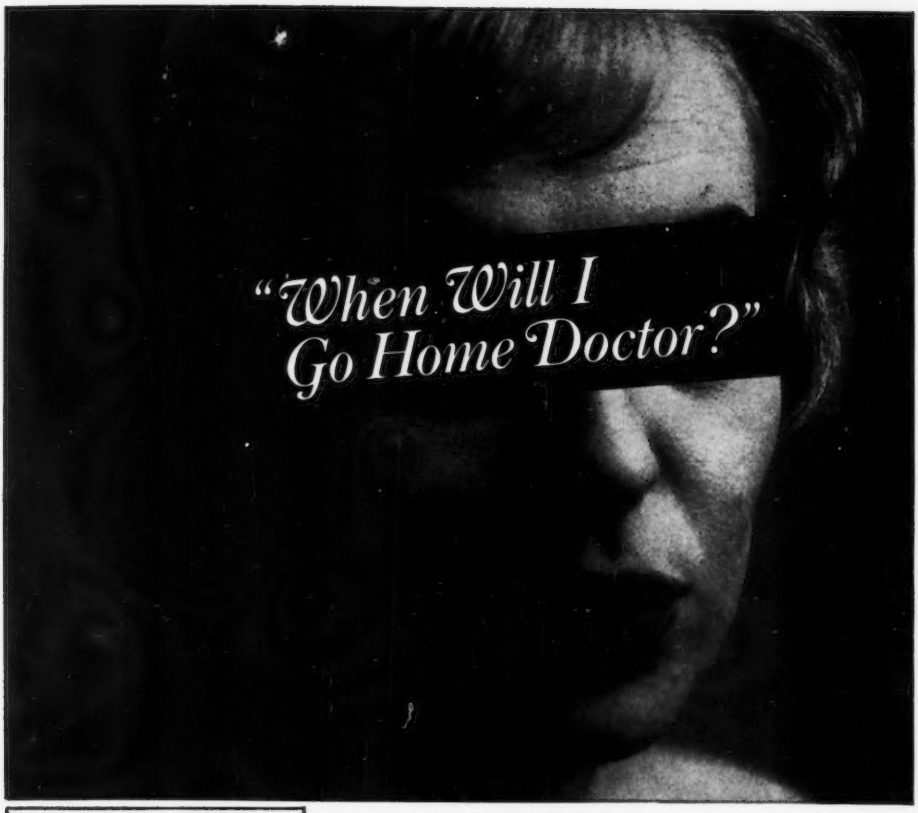

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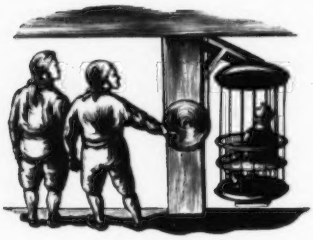

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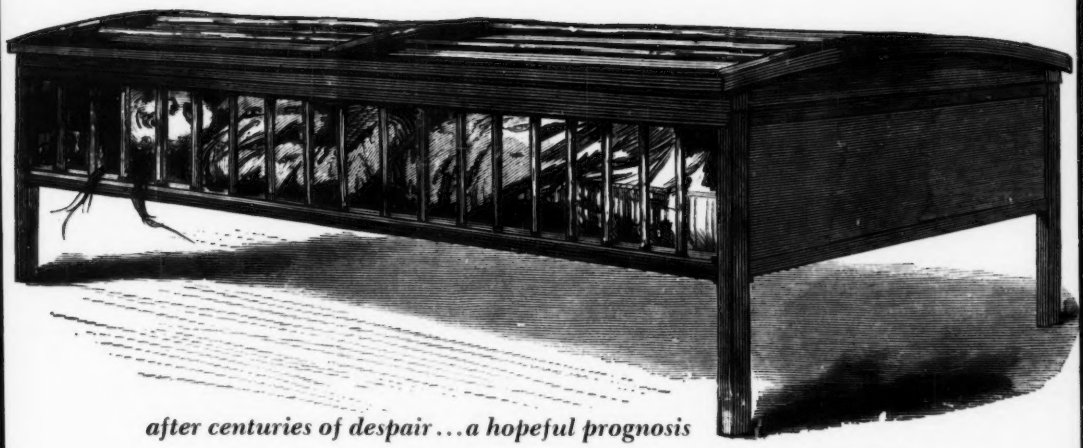

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BYRON STOOKEY, A.M., M.D., Sharon, Conn.

They who are gone are still here; though hidden they are revealed, though dead they yet speak.
—Thomas Carlyle

Osler has said: "It is good to hark back to the olden days and gratefully to recall the men whose labors in the past have made the present possible." In this spirit we celebrate today the Fiftieth Anniversary of the Neurological Institute and turn back the pages to recall our origin, paying homage to those whose trials and labors created this hospital. During the last quarter of the 19th century, New York was rich in neurological talent; there were, in fact, more distinguished neurologists here than in any other American city.

The New York Neurological Society was instituted in 1872 and reorganized in 1874, with 48 members present at its first meeting, and was the first neurological society in America. The American Neurological Association was founded in 1874, with 16 of the original 35 members from New York. The invitation to form the American Neurological Association was issued by seven men, four from New York, headed by William Hammond. The Philadelphia Neurological Society was not established until 1884, with Weir Mitchell as president, and the Neurological Society of London was not formed until 1886, having Hughlings Jackson as its president.

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Presented before the Alumni Association of the Neurological Institute, May 15, 1959, in observance of the 50th Anniversary of the Neurological Institute, Columbia-Presbyterian Medical Center.

Two of the most distinguished of our early neurologists were William Hammond, Surgeon General during the Civil War and responsible for the first Army hospital devoted to nerve injuries, and Edward Seguin, who was considered the most brilliant neurologist in America. They were aided by John C. Dalton, who held the first chair of physiology in America, at the College of Physicians and Surgeons, and also by Austin Flint Jr., whose paramount interest lay in physiology—a subject previously considered a part of anatomy. Among others were George Beard, William Browning, Landon Gray, and Edward Spitzka, the last-named bringing to early neurology a comparative anatomical concept of the nervous system, so illustriously carried on later by Oliver Strong and Frederick Tilney. These early neurologists were followed by Bernard Sachs, Allen Starr, Charles Dana, Ramsay Hunt, Smith Ely Jelliffe, and the founders of the Neurological Institute, Joseph Collins, Pearce Bailey, Frederick Peterson, and Joseph Fraenkel, all of whom had had at least part of their training abroad, bringing back with them the knowledge they had gained.

Joseph Collins, Pearce Bailey, and Frederick Peterson had worked in the Vanderbilt Clinic and held teaching positions in the Department of Neurology at Columbia under Allen Starr. The Vanderbilt Clinic, founded in 1888 by the four sons of William K. Vanderbilt, was the principal early training ground of neurologists in New York. It was directed first by Seguin, then

by Starr and Tilney. Here, as chiefs of clinic, Collins, Bailey, Peterson, Ramsay Hunt, Jelliffe, Brill, and many others received part of their neurological training. About 2,000 patients a year passed through the Neurological Clinic, where the work done was exceeded neither in quantity nor in quality in any clinic abroad. The Neurological Institute also takes pride in Charles Dana, Professor of Nervous Diseases at Cornell, whose many contributions added much to neurology in this city.

The birth of the Neurological Institute took place on the evening of March 18, 1909, when, on Dr. Joseph Collins' invitation, eight men of affairs met at the Century Club to consider the founding of a hospital for the study and treatment of nervous diseases. Those present, in addition to Dr. Collins and Dr. Fraenkel, were Mr. Isaac Townsend, Mr. R. H. Williams, Mr. Adrian Iselin, Mr. Otto H. Kahn, Mr. H. K. Knapp, Mr. Paul M. Warburg, Dr. Leighton Whitmer, and Mr. R. P. Perkins.

At this meeting the unanimous opinion was reached that an institution such as the Neurological Institute was urgently needed. An application to the New York State Board of Charities was immediately made, and on April 14, 1909, a Certificate of Incorporation was granted.

I should like to pay tribute to the devotion of the members of the Board of Trustees, who over the years stood by the hospital through many threatening problems. Without their generosity, advice, wisdom, and foresight, there would be no Institute. Our gratitude is due them as well as the medical founders.

On May 7, 1909, an organizational meeting of the incorporators was held in the office of Dr. Collins. Dr. Collins and Dr. Fraenkel were joined by Dr. Pearce Bailey, who thus became one of the founders. A letter was drafted to the Trustees explaining the ideas of the medical founders. It was pointed out that, while several neurological clinics existed, notably in Philadelphia, under the aegis of Weir Mitchell, and in New York, the Vanderbilt Clinic, as part of the College of Physicians and Surgeons at Columbia, "there was no hospital in America devoted exclusively to diseases of the nervous system. Were patients with disease of the nervous system accepted in a general hospital, no adequate staff existed to treat them, nor were the facilities available to take care of them, though such patients are as deserving as those with typhoid fever, pneumonia or any other self-limiting disease. Furthermore, due to the lack of such hospital facilities, physicians in the United States were untrained in the recognition of functional nervous or curable mental diseases, and unaccustomed to the proper and successful treatment of them." Diseases of the nervous system, no less than general medical diseases, must be taught at the bedside.

The appeal of the founders of the Institute differs only in language from the appeal made by Columbia's—then King's College's—first Professor of Physic, Samuel Bard, when in his May, 1769, commencement address he urged the necessity of a hospital, saying: "Another argument, and that by no means the least for an Institution of this Nature, is, that it affords the best and only means of properly instructing Pupils in the Practice of Medicine; as far, therefore, as the breeding of good and Able Physicians, which in all Countries and all Times has been thought an object of the highest Importance, deserves the Consideration of the Publique, this Institution must likewise claim its Protection and Encouragement."

The founders held that "the establishment of a neurological institute in New York would benefit not only those who received treatment, but would make available in this country specialized training in neurology for physicians who wished to practice and teach in this field and, above all, would be an asset to the country at large through dissemination of knowledge of the principles of neurology and nervous disease." In establishing the Neurological Institute, they had before them the example set by the National Hospital, Queen Square, begun by Miss Johanna Chandler in 1859. England's most illustrious neurologists, Jackson, Gowers, Horsley, Brevor, Buzzard, and Holmes, to mention but a few, and our

distinguished guest, Sir Francis Walshe, have all added luster to its fame.

Within a few weeks a suitable building, at 149-151 East 67th Street, was rented and alterations begun to convert it into a hospital. Drs. Taylor, Ogilvie, and Armour were engaged to serve as our first house physicians. Drs. Casamajor, from the Vanderbilt Clinic; Kennedy, from Queen Square, and Ricksher were appointed externs. The clinical laboratory was in the charge of Dr. Kaplan, who had been resident pathologist at Montefiore; the histological laboratory was under Dr. Zabriskie's direction. The consulting physicians and surgeons were Drs. Dana, Sachs, Riggs, Kinnicutt, and Abbe.

Dr. Elsberg was appointed to the Medical Board, Dec. 13, 1909, after the hospital opened, and Dr. Taylor a short time later; Drs. Beer, Neuhof, and Kenyon were made assistants to the surgeons.

While the Institute was still in its second year, a fundamental divergence of opinion arose among the three founders. Dr. Fraenkel, born in Russia, educated in Vienna, proposed that each patient, whether private, semiprivate, or ward, be treated without charge by the physician—that the hospital determine and collect the fees, and that the physician receive no compensation except from the hospital.

The issue was placed before a special meeting of the Board of Trustees on Dec. 12, 1911, in the office of Mr. Otto Kahn, who had been interested in the hospital through Dr. Fraenkel. Dr. Fraenkel resigned at this meeting, and on motion of Mr. Iselin, seconded by Mr. Kahn, the following resolution was adopted:

It is the sense of the meeting that the Neurological Institute be closed on February 1, 1912, and its affairs wound up, and that the Executive Committee be requested to take the necessary steps to carry this resolution into effect, that it further be resolved that the Secretary be directed to express to the Medical Board their sincere thanks and appreciation of the valuable services rendered by each member of the Medical Board.

Mr. Otto Kahn, Mr. Paul Warburg, Mr. Edward Devine, and Mr. Adrian Iselin Jr. resigned from the Board of Trustees.

At this critical juncture two devoted friends, Dr. Dana and Dr. Peterson, stepped into the breach—Dr. Dana, on the Board of Trustees, and Dr. Peterson, on the Medical Board. Thanks to their efforts and the loyalty of the remaining members of the Board of Trustees, the following proposal was made:

Dec. 29, 1911.

Mr. R. H. Williams, Esq., President,
Board of Trustees of the Neurological Institute
Dear Sir:

The following gentlemen, Joseph Collins, Pearce Bailey, Charles L. Dana and Frederick Peterson, understanding that the President of the Board of Trustees proposes to wind up the affairs of the Neurological Institute on February 1, have requested me to make the following proposition:

They will assume the lease of the present Institute on February 1. From February 1, they will pay half of the Superintendent's salary if he will stay in the employ of the Institute. They make this proposition with the understanding that the present building and equipment are to be turned over to them intact and that the Institute is to be absolutely free and clear of debt. It is the earnest hope and desire of these gentlemen that some of the Board of Trustees will remain on the Board to assist them in carrying on the work which has been so well done and for which the necessity is evident to everyone interested.

Yours very truly,
R. H. Perkins

P.S.: This proposition is made subject to the condition that the landlord of the Institute building is satisfied as to the clause in the present lease requiring that the building should be put back in its original form.

The remaining Trustees then resolved that the proposal as presented by the Secretary be accepted and that the Executive Committee be authorized to take the necessary steps to carry out the details.

New members were added to the Board of Trustees and at the next regular meeting, held Jan. 9, 1912, with Mr. R. H. Williams, Mr. Knapp, Mr. Mitchell, Mr. Frelinghuysen, and Mr. Townsend present, the Board expressed pleasure with the work already accomplished and authorized the President to execute a lease for a period

of three years with the owner of the Institute building.

During the second fiscal year, and each year thereafter, the number of patients increased beyond the capacity of the Institute. Collins pointed to the steady growth in the work of the Institute, saying:

> The demand by the public for what it and no other organization gives seems a final argument as to the justification of its creation and the best compliment as to the way it is run. The Institute is a machine running continuously at its highest capacity—its record is its recommendation. If that does not secure for it endowment for a suitable building no verbal solicitation will succeed.

Nevertheless, on five separate occasions, November, 1910; March, 1911; December, 1912; May, 1916, and March, 1917, ways and means committees were set up but were unsuccessful in their efforts to create an endowment and to raise funds for a new building.

The last of these committees sent letters to newspapers, accompanied by personal letters from the Trustees to the editors. Favorable editorials were written, pointing out the great service being rendered by the Institute, and 5,000 copies of the eighth annual report, for the year 1917, were issued. In this report, Dr. Collins stressed the need for greater facilities, saying: "The work that the Neurological Institute is now doing is known from one end of the country to the other." Unfortunately, this effort, begun in 1917, was thwarted by the First World War. Earlier attempts had been made to interest some of the larger foundations, but these organizations were as yet unwilling to finance completely, as they subsequently have, the creation of a new special hospital.

During these years the Institute building had been rented, with renewal of the lease from time to time; but on April 1, 1919, on expiration of the lease, the rent was greatly increased, and the following year the owner demanded that the Institute either vacate or purchase the building. Coming as it did immediately after the war, this imposed a heavy burden on a new voluntary hospital without endowment, and with a considerable deficit each year. Thus, another crisis had to be met, and under unfavorable circumstances. The staff assisted in raising part of the needed money, and on Feb. 3, 1920, the building was bought, part of the cost being covered by a mortgage.

Many problems arose in the operation of a pioneer neurological hospital. It was necessary not only to train neurologists but to meet many related special demands, such as the training of nurses in the care of patients with nervous and mental disease, the development of new methods of rehabilitation, new procedures in occupational therapy, and many other services which today are taken for granted.

Developmental Projects

Training Nurses.—Since at this time there were no graduate nurses trained in the care of patients with diseases of the nervous system, one of the aims of the Neurological Institute was to train graduate nurses to be proficient in this and cognate fields. As space in the Neurological Institute was at a premium, Otto Kahn, in the first year of the hospital's existence, generously put a house at 105 E. 75th St. at the disposal of the nurses.

A graduate nursing course of six months was begun, consisting of practical instruction in the wards and special departments. Lectures and demonstrations were given by Miss Amy Hilliard, Supervisor of Nurses. Some of these lectures were published in the *American Journal of Nursing.* Many letters of inquiry concerning the course were received during the first year, and soon the demand for this specialized training exceeded our capacity.

The nursing program thus begun continued throughout the years, producing many well-schooled and thoroughly qualified nurses to assume duties in our special fields, where previously none had existed.

Social Service Department.—This department was founded in March, 1912, by Mr. Frederick Ellis and Miss Helen Han-

nahs. In treating most of the patients seen at the Neurological Institute, a more extensive knowledge of their environment, their family background, and the social influences affecting them than could be secured by the physician was essential. This important information could be supplied by the Social Service staff. Patients who became isolated and self-centered were helped to adjust their habits and activities in terms of their nervous disorder by suggestions of the physicians, carried out through the Social Service Department. Here, again, new methods and new procedures were evolved. With Mr. Ellis, Miss Hannahs gave unstinting service until her death, in 1917. She had a masterful, far-seeing plan for the future of the Social Service Department as a place where others could be trained in this field as it particularly applied to the problems of the patients of the Neurological Institute.

Psychological and Efficiency Tests.—Among these tests, the Binet and Simon age scales, Kirkpatrick's Recall Objects, Galton's Weights Arrangements, Ebbinghaus' Sentence Completion, Thorndike's Writing Opposites, Jastrow's Free Word Production, and a number of others were studied and adapted to our particular needs. Of course, some of them have since been discarded and newer ones developed.

Occupational Therapy.—The occupational therapy department, teaching a variety of work, such as basketry, sewing, embroidery, knitting, knitted raffia, stenciling, metal work, carpentry, drawing, modeling, and bookbinding, was set up in a small house on the roof in 1910. Later in the year a printing press was added to the equipment, on which treatment cards and prescription blanks were turned out for the Institute. In the month of May during our first year, 103 patients worked in the occupational therapy department. All work completed, except that for the hospital, was taken home by the patients, whose continued efforts were followed by the Social Service staff.

Laboratory School.—In 1915 an experimental clinical school, called the Laboratory School, was founded at 157 E. 72d St., under Dr. Pearce Bailey's direction, to educate physically handicapped and scholastically backward children of superior mentality who had failed to progress in the public schools, and to determine how much could be accomplished with them by special education and to evolve methods best adapted to meet their needs. Bailey held that "the atypical child must be studied and interpreted and the possibilities that life holds for him must be defined. The faltering steps of the delinquent [must be] steadied, and the shy, the sensitive, the psychopath must be helped early."

Classification Clinic.—In 1920, under the direction of Dr. Pearce Bailey, the Classification Clinic was established at 118 E. 80th St. "for the purpose of furnishing complete physical and mental examinations to non-indigent adolescents who are failing in some way to meet what is required of them." Within a year additional space to accommodate its expanding services necessitated moving this clinic to 173 E. 70th St., where its counsel was sought on behalf of adolescents, by headmasters and headmistresses of secondary schools, and by teachers, for whom the clinic arranged a course of lectures. This classification clinic continued with great success under Dr. Bailey's direction until his death, in 1922, and then was carried on and extended under Dr. Frederick Peterson, being subsequently continued as the Child Guidance Department.

Staff Activities

In World War I, Dr. Pearce Bailey, foreseeing the possibilities ahead of us with the advent of war, obtained leave of absence in 1914 to go abroad to study injuries of the brain, spinal cord, and nerves, and the neurological and mental problems arising out of the war. By the time of our entry into World War I, he had familiarized himself with these problems and had evolved a plan of action. Surgeon

General Gorgas selected him to take charge of the nervous and mental division of the Army. In this undertaking he did outstanding work, as he had done so fully over the years for the Neurological Institute. Dr. Bailey secured an Army order providing each base hospital at the front and many tactical combat organizations with a neuropsychiatrist, a concept entirely new in medicine.*

Of the Neurological Institute's active medical staff of 37, 16 responded to the call to the colors, leaving the services very much depleted. With chiefs of service gone, the younger men who took over efficiently demonstrated the thoroughness of their training.

Two Army schools were established at the Neurological Institute to give intensive six-week courses, one in neurology and psychiatry, directed by Dr. Walter Timme, and the other in neurosurgery, under Dr. Elsberg and Dr. Taylor, with Dr. Riley as adjutant. These classes met at the Neurological Institute and at the College of Physicians and Surgeons with members of the Columbia Neurological and Anatomical Departments, Dr. Frederick Tilney, Dr. Oliver Strong, Dr. Jelliffe, Dr. Ramsay Hunt, and the Vanderbilt Clinic staff, as well as Columbia's distinguished anatomist, Dr. George Huntington.†

At the conclusion of the course in neurology and psychiatry, its members were sent to various hospitals overseas and to base hospitals in the United States to make nervous and mental examinations, to screen recruits for the Army and to take care of the neurosurgical patients.

The obvious advantages of closer cooperation between the Columbia Neurological Department, the Vanderbilt Clinic Neurological Department, and the Neurological Institute became manifest. This led to an invitation to Dr. Tilney to become one of the attendings at the Neurological Institute and a member of the Medical Board. He brought with him Dr. Charles McKendree and Dr. Henry Riley. Drs. Collins, Bailey, and Peterson had previously been members of the Columbia neurological faculty, and thus once again the two disciplines were brought together, to their mutual advantage.

In December, 1919, or 10 years after the founding of the Neurological Institute, the Board of Trustees accepted with reluctance, and with appreciation of their long service, the resignations of Drs. Collins, Bailey, and Peterson, making them consultants. Their positions as chiefs of service were taken by Drs. Zabriskie, Kennedy, and Timme. On this occasion the great indebtedness of the Neurological Institute to the founders was recorded by the Trustees as follows: "The Neurological Institute owes its origin, its growth and its development over the past ten years to their initiative and their loyal and devoted service which has given to the Neurological Institute its world-wide recognition."

The increasing demands and the continued inadequacy of the physical plant led, in the early 1920's, to discussions concerning an affiliation with the Columbia-Presbyterian Medical Center. In these deliberations Dr. Frederick Tilney was the driving force. His energy, vision, generosity, thoughtfulness, and consideration for others won the accolade of all who knew and worked with him. If the old Institute owed its existence primarily to Dr. Collins, the present Institute is equally indebted to Dr. Tilney, ably supported by Dr. Elsberg and Dr. Zabriskie.

* On March 12, 1921, Bailey was awarded the Distinguished Service Medal: "For exceptionally meritorious and distinguished service as Chief of the Division of Neuropsychiatry, Surgeon General's Office, in which capacity he displayed exceptional zeal, foresight, and good judgment in organizing, developing and directing neuropsychiatric work in the Army on a high plane of efficiency."

† It is interesting to note that Columbia's medical school served a similar function during the Civil War. Special courses in military surgery and hygiene were conducted at the request of the Surgeon General's office from 1862 to 1865.

In the development of the plans for the hospital to become a unit in the Columbia-Presbyterian Center, Dr. Tilney, in 1921, created within his own department a chair of Experimental Neurology, to which he appointed Dr. Elsberg, and two years later the title was changed to Professor of Experimental Neurology and Experimental Neurosurgery. After the plans to move to the Medical Center were consummated, Dr. Allan Whipple, head of the Department of Surgery, appointed Dr. Elsberg to the surgical department as Professor of Neurosurgery.

The affiliation with Columbia and the Presbyterian Hospital involved numerous problems and contending loyalties; however, after many conferences, these were finally resolved, and on Feb. 24, 1925, a combined meeting of the medical staff and the Board of Trustees of the Neurological Institute was called and the conclusion reached that the best interests of the Neurological Institute would be served by moving to the Columbia-Presbyterian Medical Center. On March 10, 1925, this affiliation was ratified. This, regrettably, resulted in the resignation of a steadfast and cherished friend of the Institute, Dr. Charles Dana, Professor of Nervous Diseases at Cornell.

Building plans were immediately drawn, and on Oct. 19, 1927, ground was broken, the Medical Center having given the land upon which the present building stands. Originally 10 stories were contemplated; but, after further deliberation, it was decided to build 4 additional floors. In June, 1929, the Neurological Institute opened its new building. At last it had achieved its long-cherished desire for adequate modern facilities, enabling it to give the utmost to those suffering from nervous and mental diseases and to push forward its services as a teaching center, thus fulfilling the purpose stated by Dr. Collins in the first year of the hospital's existence: "The vital element of our work is educational, so that throughout the country great profit shall come to all mankind through the ministrations and example of those who are taught here in special fields."

A building worthy of its aims had finally arisen, and the Neurological Institute, with its laboratories, became closely associated with the State Psychiatric Hospital, with its laboratories, and the medical and research facilities of Columbia and the Presbyterian, to the greater advantage of all concerned. At this time the Institute looked forward to establishing an adequate endowment, not only to cover its running expenses but to enable it to carry forward research; however, a few months after the Institute opened, the depression of 1929 struck, and the hospital in the ensuing years was again faced with one deficit after another, differing from previous deficits only in their magnitude. These had to be met and finally were assumed by the Presbyterian. Without this generous support, the Institute would have failed. The Trustees and the Medical Board during these years would have sympathized with the Dean of Oxford University, when, after repeated efforts to raise money, on Oct. 23, 1426, he appealed to the Duke of Gloucester for funds, saying: "Let not poverty, that cursed stepmother of learning, disappoint us of our hopes."

Our Neurological Institute has much to be proud of. It was the first neurological hospital on this continent and pioneered the first training school for nurses in this field; it developed special social service workers and occupational therapists, created the Laboratory School for defective children and the Classification Clinic, and established many other innovations. The spiritual values which it has so generously given will long endure. Even before it became of age, it was recognized as a great institution. It remains deeply imbued with neurological and neurosurgical skills, which its founders so generously instilled. It brought with it, and has continued to bring to the Columbia-Presbyterian Medical Center, distinction and a heritage of which those who have trained here, and we who

have been privileged to work here, may well be proud. Carlyle has said: "All work is as seed sown; grows and spreads and sows itself anew." Thus, it is to you who have trained here to carry on; and if I may complete the title of this paper, taken from Shakespeare's "Tempest": "What is past is prologue; what to come in your discharge."

Sharon, Conn.

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Familial Periodic Paralysis

Report of a Case Resistant to Dextrose and Insulin Provocation

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Familial periodic paralysis is a disease of unknown etiology characterized by recurrent acute attacks of weakness associated with a fall in serum potassium levels. The syndrome of acute and/or repeated paresis, however, can be brought on by a variety of factors, which must be distinguished from those in familial periodic paralysis. Hammes [1] considers that the commonest causes of acute paresis are poliomyelitis, hysteria, the Guillain-Barré syndrome, postdiphtheritic neuritis, tic paralysis, porphyria, and necrotizing myelitis. In addition, he reports three cases of familial periodic paralysis in which the disease was misdiagnosed as poliomyelitis, malingering, and myasthenia gravis, respectively.

Muscular weakness may result from both hypokalemia and hyperkalemia. Milne, Stanbury, and Thomson [2] observed a patient with the Fanconi syndrome who lost potassium excessively and whose condition had actually been diagnosed as familial periodic paralysis until the true picture was revealed. Attacks of flaccid paralysis were seen in the patients of Fitzgerald and Fourman [3] and Jackson and Oakley [4] secondary to pyelonephritis and hypokalemia. A case of pyelonephritis following ureterosigmoidostomy has been reported [5] as developing hypokalemic paralysis. Evans and Milne [6] report a case of "potassium-losing nephritis" which presented as familial periodic paralysis but with attacks lasting up to 20 days, a longer period than is seen in periodic paralysis. Conn [7,8] has criticized this paper from the point of view of the possibility that the patient may actually have had primary aldosteronism, in the first reported case of which recurrent paralysis was also present. Brooks, McSwiney, Prunty, and Wood [9] reported a case of an adrenal tumor which responded to corticotropin and caused paralysis through excessive electrolyte loss. Likewise, Campbell, Nicolaides, and Steinbeck [10] report a case of adrenocortical tumor associated with hypertension, flaccid paralytic attacks, and hypopotassemia reaching levels of 2 mEq/L. Strong [11] and Cayley [12] report paralysis following the ingestion of aminosalicylic acid in a licorice base, which may have had some desoxycorticosterone acetate (DOCA)-like action in causing salt loss. Kjerulf-Jensen, Krarup, and Warming-Larsen [13] report a case in which, following a bout of lymphocytic meningitis, an endocrine imbalance developed, possibly secondary to a hypothalamic lesion. Persistent hypokalemia with paralytic attacks developed. Paralysis may occur during treatment of diabetic coma when potassium is not vigorously replaced.[14,15] Inadequate potassium intake was the basis of Smith's method [16] of devising an animal analogue of familial periodic paralysis. Feeding dogs a low-potassium diet coupled with a deficiency in B-complex vitamins, she was able to produce such typical signs as bradycardia, a striking fall in potassium, and creatinuria in paralytic attacks produced by epinephrine.

A similarity between hyperkalemic paralysis and periodic paralysis was noted by Finch and Marchand in a patient overtreated with potassium chloride as a diuretic.[17] Bull, Carter, and Lowe [18] have reviewed the subject of hyperkalemic paralysis and reported three patients with such a syndrome second-

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From the Second (Cornell University) Neurologic Service, Bellevue Hospital, and Cornell University Medical College.

ary to glomerulonephritis, Addison's disease, and renal tuberculosis, respectively. Mollaret, Goulon, and Tournilhac [19] have also discussed the subject and report a case of adrenal insufficiency and hyperpotassemic paralysis. In general, paresthesias occur, contrary to their absence in periodic paralysis, and the distribution of weakness is similar to that in Landry's ascending paralysis, with occasional involvement of facial muscles. Usually, the duration of paralysis is longer and does not occur in paroxysms. Sandkühler,[20] however, reports a patient who exhibited periodic seizures with potassium as high as 41.4 mg. % on one occasion.

A recently christened disease, "adynamia episodica hereditaria," [21] can be confused with familial periodic paralysis. Tyler, Stephens, Gunn, and Perkoff [22] studied a group of 33 related people with periodic paralysis and found no relation between potassium and the attacks. Furthermore, there was no relief of symptoms with potassium. Genetic study of this group was complicated by the fact that they were Mormons practicing polygamy. However, the authors were able to determine that the disease was passed as a simple dominant with complete penetrance. Another large group of victims (65) not responding to potassium therapy was reported by Sagild and Helweg-Larsen.[23] From the Los Angeles Children's Hospital [24] came the report of a mother and her three children who suffered paralytic attacks without response to potassium and without depressed serum potassium levels. Kaplan, Straus, Grumbach, and Aymard [25] report a few such cases and tabulate the differences between familial periodic paralysis and adynamia. Gamstorp, in her monograph [21] on the subject, summarizes the findings culled from 138 known cases, 68 of which she examined herself. The disease came on before the age of 10 years in over 90% of the patients, and attacks lasted about an hour. Half the patients showed weakness of muscles innervated by the cranial nerves. Exercise helped to ameliorate the attack, as did food. Deep tendon reflexes were absent in over half the patients, and yet there were many who had a positive Chvostek sign. Potassium chloride was found to be almost uniformly successful in *provoking* attacks. Calcium given intravenously was found to control the seizures. Dextrose and insulin ameliorated attacks. As for the level of potassium, Gamstorp et al.[26] report that in over 50% of attacks the potassium exceeded 5.5 mEq/L. Electomyography showed patterns similar to those in periodic paralysis. The prognosis was good, and, like classic periodic paralysis, adynamia tended to show improvement after the age of 30. The authors postulate that the disease involves excessive leakage of potassium from the cells, although there are no biopsies as yet. Because an acutely paralyzed patient may have adynamia, serum electrolyte determinations should be done before giving potassium.

In contrast to the above conditions, familial periodic paralysis has a distinctive clinical picture, delineated in Talbott's review.[27] The following case is an illustrative one, in which the patient showed resistance to dextrose and insulin provocation.

Report of Case

A 14-year-old white schoolboy was brought to the Bellevue Hospital emergency ward at 2 a. m. on Jan. 26, 1958, because of inability to move his arms and legs.

The patient's illness dated back two and one-half years, when recurrent attacks of flaccid weakness had their onset. These episodes always came on after the patient retired to bed and occurred only in the winter months. At this time, signs of puberty made their appearance, e. g., acne vulgaris, deepening of the voice, and sexual development. The attacks usually followed large dinners on weekend nights, when the patient would eat fried chicken, mashed potatoes, pastries, and sweets. The attacks never occurred on Tuesday, Wednesday, or Thursday. The commonest time for the seizures was between 2:00 and 5:00 a. m. The patient usually would awaken from sleep, conscious of a "numb sensation" in his legs. This would spread next to his arms and finally to the trunk, and he would be unable to turn over in bed. Sometimes, if he awoke early enough, he was able to abort the paralysis by getting up and mov-

ing about. Respiration, speech, and sense perception were never affected. Occasionally, the patient would benefit from passive motion, application of warm rags, or warm tea. The attacks were increasing in frequency and severity. Whereas in the beginning the paralysis lasted only 2-6 hours, as a rule, and often could be aborted, the patient at the time of admission was having one to two attacks each week lasting up to 36 hours, involving complete quadriplegia. Two weeks before admission, the patient was seen at another hospital during the recovery phase of an attack, and a diagnosis of Raynaud's disease was made on the basis of the relationship of the attacks to cold weather. A series of histamine injections was ineffective.

On the evening of admission, the patient retired to bed after a large meal of fried chicken, potatoes, and cake ala mode. At approximately 10 p. m., he noted onset of weakness, which progressed to total quadriplegia in an hour and a half despite attempts at active movement. The patient felt nauseated, vomited, and complained of dyspnea. The parents became alarmed, and the patient was brought by ambulance to the hospital.

The family history revealed that the patient's parents were well, except that his 40-year-old mother had always had attacks of weakness in her arms. These attacks were said to be unilateral at times, worse during cold weather, easily aborted by active motion, and becoming less frequent with age. Two uncles on the mother's side, living in Europe (the family was Ukranian), aged 25 and 18, were said to suffer from paralytic episodes, similar to those of the patient. The patient's father and 10-year-old brother were free from attacks.

Physical examination revealed the patient to be a well-developed adolescent boy of muscular build, who was apprehensive and complained of dyspnea in the supine position. Blood pressure was 130/70; pulse, 100 a minute; respirations, 14 a minute, and temperature, 37.6 C (99.7 F). Respiration was noted to be deep and labored. Acne vulgaris and normal male pubic and axillary hair were present The chest was clear, and no cardiac abnormality was present. The abdomen was soft, and the patient could urinate on request. Neurological examination revealed almost complete flaccid quadriplegia, and deep tendon reflexes were unobtainable. He was barely able to move his toes and fingers. There was no decrease in sensory perception, and he cried out when blood was drawn, but there was no withdrawal. The muscles innervated by the cranial nerves were intact. Hemogram and urinalysis were normal.

A medical resident gave 20 mEq. of potassium chloride intravenously on the chance that the patient might have familial periodic paralysis. Unfortunately, no blood was taken for electrolyte analysis. The patient immediately improved and was able to stand in two hours. The following day he was walking about the ward normally; yet examination showed absence of the biceps, triceps, pectoral, radial, and ulnar reflexes, and the knee jerk was 1+, the ankle jerk 2+, bilaterally, and the plantar response was flexor bilaterally. All reflexes reverted to normal later in the day.

An electroencephalogram showed asymmetry, with 2-3 per second and 4-7 per second activity in the left hemisphere.

On the following days the patient was subjected to various provocative tests. On Jan. 30, dextrose, 125 gm., was given orally, and potassium fell from 4.1 to 3.4 mEq/L., but no weakness was noted. The following day, 1 liter of 20% dextrose and water with 40 units of regular insulin was given intravenously over three hours; but, although the serum potassium fell to 2.9 mEq/L., there was again no weakness. On Feb. 3, 150 gm. of dextrose was given orally and 20 units of regular insulin injected subcutaneously before allowing the patient to go to sleep next to an open window. This measure also failed, and the patient was discharged on Feb. 7, 1958.

On Feb. 19, 1958, the patient was readmitted with weakness, of two hours' duration. During the previous two days he had come down with "grippe," consisting of headache, fever, and slightly productive cough. On admission, physical examination revealed the blood pressure to be 160/90, pulse 80, respiration 20, and temperature 38 C (100.4 F). There was weakness of the arms and legs, and the reflexes were hypoactive and equal on the two sides. The neck muscles were weak, and the patient could not urinate. Laboratory findings were normal except for a corrected sedimentation rate of 24 mm/hr. and a white blood cell count of 10,000, with a normal differential. The BUN was 13 mg. %; sodium, 147 mEq/L.; potassium, 2.0 mEq/L., and phosphate, 2.4 mg. %. He was given 40 mEq. of potassium chloride in a glass of orange juice, and immediately began to show improved muscle function. One hour after admission and after administration of potassium, the serum potassium was 2.3 mEq/L. At this point the patient was able to walk. Six hours after admission, serum potassium was 2.4 mEq/L., and seven hours after admission it was 2.7 mEq/L. By then, full muscle strength had returned. A repeat electroencephalogram on this admission showed the same pattern. His mother and 10-year-old brother were given 125 gm. of dextrose orally. The mother's potassium fell from 3.6 to 3.2 mEq/L. and the brother's fell from 3.4 to 3.1 mEq/L., but no paralysis resulted. The patient was discharged on Feb. 22, 1958, and was told to take 3 gm. of potassium chloride before bedtime on weekend nights and whenever he felt the onset of weakness.

On March 17, 1958, the patient was seen in the emergency ward with total quadriplegia following a heavy meal. He had been unable to abort the attack with 5 gm. of potassium chloride. Given 3 gm. more by mouth, he recovered sufficiently to be sent home.

On June 20, 1958, the patient was admitted for the third time for weakness. He had not taken prophylactic potassium for several weeks because he had never been stricken with an attack this late in the year. On this occasion, the patient showed the usual flaccid paralysis and absence of deep tendon reflexes; abdominal reflexes also were absent. A soft, blowing systolic murmur was heard in the pulmonic area, radiating to the neck. The patient was catheterized to relieve bladder discomfort. The electrocardiogram showed predominantly flattening of the T-waves. Serum potassium was 2.0 mEq/L. He recovered after ingesting 3 gm. of potassium chloride dissolved in orange juice. The following day, serum potassium was 5.6 mEq/L., and there was no evidence of cardiac murmur or electrocardiographic abnormality. He was discharged on June 24, 1958.

On July 6, 1958, the patient was admitted for the fourth time with paralysis, which had not been prevented by active motion and 3 gm. of potassium chloride. Blood pressure was 120/50, pulse 86, respirations 18, and temperature 38 C. The electrocardiogram showed low or isoelectric T-waves in Leads III, aV_F, and V_3 to V_6, and prominent U-waves in Leads V_3 through V_6. No treatment was given, and the patient recovered spontaneously over a period of 10 hours. On admission, serum sodium was 148 mEq/L., serum potassium 3.1 mEq/L., and serum chloride 107 mEq/L. After recovery, serum potassium was 6.0 mEq/L., serum sodium 144 mEq/L., and serum chloride 101 mEq/L. He was discharged on July 8, 1958.

At present the patient is well and maintained on 1 gm. of potassium chloride a day except for weekend days, when he takes 3 gm. He has been cautioned to refrain from overeating and to avoid rich, salty foods.

This patient exhibits many characteristic features of familial periodic paralysis, among which several are to be noted. 1. Familial history. Sporadic cases are not uncommon, however. Herrington[28] in 1937, estimated that 80% of victims gave a family history of the disease; but this figure was based on a relatively small number of cases, and the exact percentage is not known. 2. Onset of symptoms with puberty. 3. Occurrence of severer attacks in cold weather and absence of attacks during the summer. 4. Frequency of attacks at night. 5. Precipitation of attacks by heavy meals. 6. Abortion of attacks by active and passive motion. 7. Typical distribution of the paralysis, starting in the proximal portions of the extremities. 8. Precipitation of attacks by upper respiratory infections. 9. Electrocardiographic abnormalities. 10. Low potassium levels, reaching 2.0 mEq/L. on two occasions, and still low in the recovery phase (2.4-2.7 mEq/L. during the second admission). 11. Low phosphate concentration during an attack. 12. Effectiveness of potassium chloride in terminating an attack. 13. Ineffectiveness of ingested potassium in preventing attacks in the absence of adequate dietary restrictions. 14. Misdiagnoses, including "Raynaud's disease" and "conversion reaction." Familial periodic paralysis has been mistaken for psychogenic syndromes before; indeed, Talbott[27] cites a case of a Russian soldier killed by his comrades for "malingering." It is believed, however, that this is the first time this disease has been misdiagnosed as Raynaud's disease.

Among the less typical features here was the respiratory involvement, which is known to occur, but only in severe attacks. It is probably the commonest cause of death in this disease.[27,29] In a case reported by Kosonen,[30] a respirator had to be used. The mother's history of unilateral attacks in the arms is atypical, since the legs are usually affected first, and attacks are almost always bilateral, although exceptions have been recorded.[31] The electroencephalogram was considered abnormal; but, while this is unusual in periodic paralysis,[32] about 10% of normal people have abnormal electroencephalograms.[33]

The difficulty in producing attacks, despite such harsh measures as intravenous dextrose and insulin, is of some interest. Recent work by Conn and his co-workers[34] has shown that patients may be protected from the provocative effect of dextrose and insulin by limitation of sodium intake. The present patient was subjected to a routine hospital diet for three days before attempts were

made to provoke attacks. Such diets, consisting of 1,800-2,500 Cal. per day, may contain as little as 5 or 6 gm. of sodium chloride.[35] Whereas the patient readily suffered paralytic seizures at home, inadvertent limitation of sodium during the course of his admission probably resulted in increased resistance to dextrose and insulin. This assumption is further supported by the failure of potassium chloride to stop severe attacks in the absence of dietary admonitions, whereas the patient has remained asymptomatic after being told to limit his intake of rich, salty foods.

Comment

It was Aitken, Allott, Castleden, and Walker,[36] in 1937, who noted that a fall in serum potassium was a prominent and constant feature of an attack of periodic paralysis. Biemond and Daniels[37] had recorded a rise in potassium following an attack, but stated: "Most investigators believe that it is a question of some toxic process." Aitken et al.[36] postulated that the fall in potassium was directly related to a block in neuromuscular conduction or muscular contraction. Grob, Johns, and Liljestrand[38] feel that there is a derangement of the normal ratio between intracellular and extracellular potassium concentrations, i. e., $[K_i]/[K_o]$, which is largely responsible for the resting muscle-membrane potential. During an attack, $[K_o]$ decreases, owing to a movement of potassium into the cells, rendering the membrane hyperpolarized and impervious to depolarization by direct, electrical, or acetylcholine stimulation. Johns, Liljestrand, Grob, and Harvey[39] have also demonstrated a partial neuromuscular block due to resistance of the motor end-plate to depolarization. Since the membrane potential of nerves is also dependent on potassium concentrations, one might ask whether the paralysis is partially neurogenic. However, there is no sensory disturbance in this disease, and the electromyogram typically shows patterns similar to those in primary muscle disorders.[40] Kugelberg[41] has found that the muscle involvement is more diffuse in periodic paralysis than in neurogenic lesions, which show correspondence to motor units. Both Petersén and Widén[40] and Kugelberg[41] have noted the shortening of spike potentials in this disease down to the range of 1-3 msec. Merton[42] mentions that the electromyogram in periodic paralysis is similar to that in fatigued muscle. It was through electromyography that the peripheral nature of the lesion was confirmed by Gammon and Harvey[43] in 1941. These authors traced the rise in stimulation threshold as an attack developed, using the fifth short flexor of the hand to record from while stimulating the ulnar nerve. Gass, Cherkasky, and Savitsky[44] have suggested that the contractile mechanism may be affected by intracellular binding of potassium.

Stewart, Smith, and Milhorat[45] were the first to give electrocardiographic evidence of heart involvement in this disease, and demonstrated the pattern changes of hypopotassemia. Van Buchem[46] postulates that there is a drawing in of potassium into the skeletal muscle cells, leaving the myocardium relatively deficient; i. e., the involvement of the heart is due to an intracellular lack of potassium, while the opposite is true in skeletal muscle.

The loss of potassium from the intravascular space was at first an enigma, and some authors thought that it was lost through the urine. Careful balance studies by Gammon et al.[47] and also by Ferrebee et al.[48,49] showed that there was actually a retention of potassium, and sometimes also of water. Gass et al.[44] confirmed the salt and water retention in their patient. The logical supposition was that potassium entered the cells during an attack. Cumings, in biopsy studies of various muscle disorders,[50-52] has found a high potassium content in muscle in periodic paralysis, as well as in myasthenia gravis, and a low potassium in myotonic muscle. Vastola[53] biopsied muscle between and during attacks of periodic paralysis and found that, while there was no demonstrable difference in the *concentration* of potassium

in the samples, there was a 39% increase in potassium content expressed in terms of dry muscle weight. This indicates that there is movement of fluid as well as potassium into the cell. Earlier biopsies, such as those by Crafts,[54] Zabriskie and Frantz,[55] and Allott and McArdle,[56] revealed vacuolation of muscle cells, interpreted as pockets of newly formed intracellular fluid.[57] Clinically, it has been said that the muscles feel firm despite the flaccid paralysis,[27] presumably owing to an increased fluid content. Neel[58] showed marked differences in the circumferences of the limbs of his patient during and after an attack. Conn et al.,[34] in biopsies, also noted the increased potassium and fluid content, as well as an increased intracellular sodium. Because of fluid movement into the cells, one might expect contraction of the extracellular fluid volume, but this was not demonstrable by Danowski et al.,[59] using the mannitol method. This is not surprising, since there is probably an increase in total body fluid, urine volume falling to as little as 660 ml. a day in some instances,[44] and recovery is accompanied by diuresis.[34]

Conn and his co-workers[60] have recently reawakened interest in sodium metabolism in this disease. Serum sodium has been observed to rise during the attack,[27] although it is a relatively small elevation in comparison with the fall in potassium. In the patient studied by Conn et al.,[60] an attack was heralded by an impressive increase in aldosterone secretion, followed by sodium and water retention. Since potassium retention and paralysis occurred somewhat later than this, and sodium diuresis occurred before potassium diuresis in the recovery phase, these authors suggest that sodium is even more significant than potassium. Further evidence for this was presented in a later study.[34] It was demonstrated that a diet containing only 8 mEq. of sodium per day protected the patient from attacks induced by dextrose and insulin, whereas a diet with 208 mEq. per day did not. Potassium and other factors were kept constant, since Ziegler and McQuarrie[61,62] have demonstrated that susceptibility to attacks is dependent on a variety of factors. Interestingly, although dextrose and insulin produced no paralysis with the patient on a low-sodium diet, the characteristic increase in aldosterone production occurred.

Although recurrent paresis is the most obvious manifestation of this disease, it is clear that there are abnormalities during "well" periods. Grob et al.,[38,63] by the technique of measuring arteriovenous differences in potassium concentration, showed that victims of this disease have an anomalous response to insulin. Whereas normal subjects lost potassium from muscle when given insulin,[63] presumably because of deposition of this cation with glycogen in the liver,[64] there is an increased muscular uptake of potassium in periodic paralysis. McArdle[65] has described experiments in which the arteriovenous difference in potassium concentration in patients with familial periodic paralysis was measured during and after exercise. These patients took up 15 times as much potassium as the controls after work, having lost an inordinate amount during exercise. This technique has shown abnormal potassium uptake before an attack and leakage of potassium in the recovery phase,[38] but McArdle's experiments showed an abnormality between attacks. Coupled with the fact that pyruvate and lactate levels after exercise were two and one-half times normal, and the fact that phosphate usually falls along with potassium concentration during an attack, McArdle's experiments seem to point to a defect in carbohydrate metabolism. Allott and McArdle[56] have postulated a block in glycolysis at the hexose phosphate level. Potassium would then move into the cell to neutralize the impermeable organic anions in accordance with the theory of Conway and Boyle.[66] Other lines of evidence that there is something wrong even during "normal" periods arise from observations by Conn et al.,[34,60] who noted that their patient exhibited intermittent aldosteronism between attacks. Also, administration of a

mineralocorticoid, 2-methyl-9-α-fluorocortisone, produced both sodium and potassium retention in this patient, whereas in normal people there is a sodium retention and potassium loss.

It has long been noted that patients with periodic paralysis have clinical weakness at potassium levels which do not affect other subjects.[56] Practically any measure to lower serum potassium will provoke an attack, and such tests have become popular often without any purpose aside from confirmation of the diagnosis. Such measures include administration of dextrose and/or insulin,[67] water diuresis,[47] ingestion of ion-exchange resins,[68] epinephrine,[47,69,70] thyroid extracts,[71] and corticotropin.[65] Hypermetabolic situations, such as exposure to cold, excitement, and infections, may bring on attacks possibly by lowering potassium level. These facts per se indicate little more than that the periodic paralytic is more sensitive than usual to low potassium concentrations. Demonstration of paralysis by local cooling of an extremity by Zabriskie and Frantz [55] and Ziegler [72] has not been fully explained, but McArdle,[65] who confirmed these results, indicates that there may be some alteration of membrane equilibrium brought about by interference with metabolic processes.

The increased frequency of attacks during the night is a long-recognized feature of familial periodic paralysis,[27] and is demonstrated by the patient. Obvious factors may be responsible here, such as the lower temperatures at night, the lack of motion during sleep, and the fact that a large meal may have been ingested shortly before retiring. Metabolic changes which occur during sleep are reviewed by Robin,[73] who notes that fully 70% of the daily production of corticosteroids occurs between the hours of 12 and 7 a. m. Perkoff et al.[74] recently have presented evidence that increased secretion of corticotropin is the basis for this diurnal variation. Conn et al.[34] have produced an attack with a synthetic mineralocorticoid, while McArdle [65] brought on severe paresis with corticotropin. Increased steroid production may therefore at least reinforce the tendency toward more frequent nocturnal attacks. On the other hand, aldosterone production has been shown to be greater in the day than at night,[75] but no similar studies have been reported on patients with periodic paralysis. Zierler and Andres [76] observed that a shift of potassium into muscles at night took place in normal people, with extrusion of potassium taking place by midmorning. In their two patients with periodic paralysis, they found that the rate of potassium movement was 5 to 10 times normal. These interesting results could be explained on the basis of an increased secretion of steroids or an abnormal response to a normal rate of secretion.

Brief mention should be made of the occurrence of periodic paralysis in various thyroid disorders and the possible etiologic significance of such a relationship. Shinosaki [71] reported on the first patients in 1921, most of whom had hyperthyroidism, while a few had simple struma. In the first English-language article on the subject, Dunlap and Kepler [77] reported on seven patients with periodic paralysis, four of whom were hyperthyroid. Hildebrand and Kepler [78] observed a patient who seemed to have classic periodic paralysis as a child but appeared to have "outgrown" the disease. He later developed thyrotoxicosis, a recurrence of paralytic attacks, and was cured by thyroidectomy. The authors speculate that there is some direct effect of the thyroid on muscle, rendering it susceptible to periodic paresis, since thyroid goiter is not usually associated with marked hypopotassemia. Lindner [79] has reviewed the now substantial literature on this subject and cautions that periodic paralysis may be an early sign of hyperthyroidism. This is further borne out by the recent report of Okinaka et al.,[80] who summarize the experience in three Japanese hospitals, where, out of 6,333 patients with hyperthyroidism, 1.9% had attacks of periodic paralysis. Among 1,214 males the incidence was 8.2%, whereas it was only 0.4% in females. The authors

found that fully 27% of those developing periodic paralysis did so before the onset of thyrotoxic symptoms. These studies again emphasize the difficulty in deciding whether or not there is some abnormality basic to both classic and thyrotoxic periodic paralysis. Adams et al.[57] consider the two to be separate diseases, and McArdle[65] has the impression that potassium levels fall farther in thyrotoxic periodic paralysis. Clinically, however, the diseases are indistinguishable except for the symptoms of thyroid disease; and more studies are needed to clarify the interrelationship of thyroid, adrenal, and muscle in periodic paralysis.

Summary

Familial periodic paralysis must be distinguished from a variety of acute paralytic syndromes, among which are both hypokalemic and hyperkalemic conditions.

The case of a 14-year-old youth with the classic signs of familial periodic paralysis is presented. Although attacks developed at home with great frequency, this patient exhibited resistance to the provocative effects of dextrose and insulin in the hospital. It is inferred that this resistance was due to a relatively low sodium intake while on a routine hospital diet. The patient experienced attacks despite potassium prophylaxis, but became asymptomatic after receiving dietary admonitions.

There is evidence that the fall in serum potassium brings about paralysis by altering muscle-membrane potential. Clinical, histological, and metabolic studies suggest fluid and electrolyte changes, mediated by a hormonal abnormality. Greater frequency of attacks at night supports this view.

Periodic paralysis associated with hyperthyroidism seems closely related to classic familial periodic paralysis, and there may be some interplay between thyroid, adrenal, and muscle in this disease.

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Spinal Cord Convulsions

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The motor manifestations of maximal seizures have similar patterns in man and most laboratory animals.[1] Since the motor pattern itself, apart from electrical correlates of convulsive activity, provides diagnostic guides in clinical epilepsy, as well as useful end-points in research on convulsive disorders, elucidation of the neural determinants of the convulsion pattern is of basic significance. Studies on the determinants of the motor pattern have largely centered around stimulation of specific supraspinal areas and correlation of electrical activity of the brain with motor behavior. The reflex mechanisms of the spinal cord have received little attention, and the majority of investigations have, by implication, assigned a passive role to the cord. The importance of spinal reflexes in determining the seizure pattern was shown by recent experiments from this laboratory,[2] in which it was demonstrated that the maximal seizure pattern is profoundly modified by dorsal-root section. The results of these experiments led to the present study, in which the entire spinal cord was stimulated in decapitate animals. While such stimulation may have no precise counterpart in either epileptic or electroshock seizures, the fidelity with which the maximal *(grand mal)* seizure pattern may be reproduced suggests that the final integration of the supraspinal seizure discharge into the motor pattern is accomplished by the reflex mechanisms of the spinal cord.

Methods

Tracheal cannulation and section of the spinal cord through an incision at the atlanto-occipital junction were performed under ether anesthesia. After section below the medulla, the animal was maintained on artificial respiration. In some experiments cerebral structures were destroyed by ligating the carotid arteries and clamping the vertebral arteries. From 30 to 60 minutes was allowed for elimination of the ether. The stimulating electrode was of stainless-steel wire, insulated except for the portion in contact with the spinal cord. The noninsulated portion, about 4 cm. long (cat and rabbit), was inserted into the cord from about C-1 to C-4. Proportionately smaller electrodes, similarly placed, were used for rat, hamster, and mouse. The cord electrode was the cathode; the anode was attached to surrounding tissues. Square-wave stimuli were delivered by a Grass stimulator. Maximal-stimulus parameters, in terms of the intensity of the motor response, were found to be 1-2 msec. and 30 to 50 volts. With maximal stimulation the entire cord was stimulated, and both hindlimbs moved in synchrony, even if the electrode was placed along one side of the cord. Motor patterns were observed for the hindlimbs only, since there was a component of direct stimulation to forelimb nerves.

After determining the parameters required for supramaximal stimulation, motor responses were studied only as a function of stimulus frequency. Simple motor sequences, such as the flexor-extensor convulsion, were timed by visual observation. Records of complex motor events, such as reciprocating stepping movements, were made on a Grass polygraph by means of strain gauges.

Maximal electroshock seizures were elicited by supramaximal brain stimulation for 0.2 second with a 60-cycle alternating current electroshock apparatus.[3] Corneal electrodes were employed with all species.

Results

The hindlimb motor patterns in response to spinal cord stimulation at C-1 to C-4 were examined at stimulus frequencies of from 1 to 300 per second. Figure 1 gives the duration of each phase of the convulsion during continuous stimulation in the cat. At low frequencies (below about 10/sec.) running and clonic movements are observed. At frequencies between 10/sec. and 40/sec. the hindlimbs are maintained in tonic flexion.

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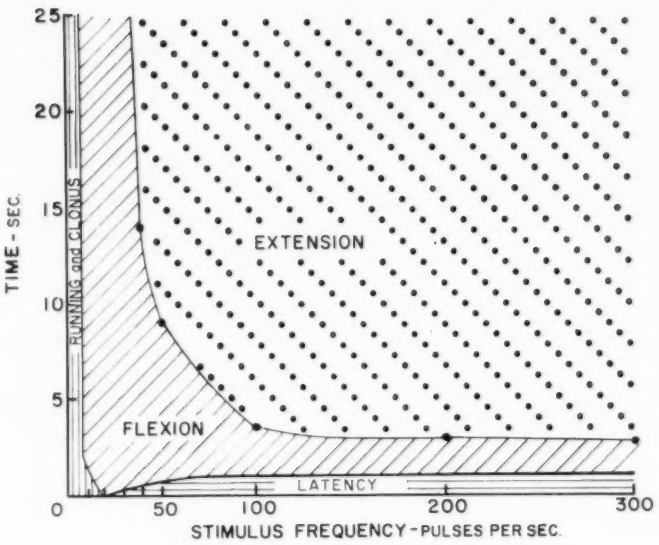

Fig. 1.—Hindlimb responses of the cat to continuous supramaximal spinal cord stimulation at various frequencies. A vertical projection from any stimulus frequency on the abscissa intersects the fields representing the successive phases of the convulsion. The duration of each phase is given by the time values, on the ordinate.

In some animals the flexion is interrupted by brief extensor thrusts. At still higher frequencies, flexion changes abruptly to rigid hindlimb extension, and the pattern closely resembles that of the maximal seizure of the intact animal. As frequency of stimulation is increased, the time to extension diminishes. It can be seen that the flexor phase at high-frequency stimulation is preceded by a latent period. During this phase, which lasts about 1.5 second, the hindlimbs show no response, either tonic or clonic, to the stimulus. Stimulation of the cord through an electrode inserted at T-3 results in the same motor sequences as depicted in Figure 1.

The pattern of motor events shown in Figure 1 has been observed, with only minor variations, in each of 22 cats examined. The electroshock seizure pattern in intact cats is not so constant; about 30% of animals (flexor cats) characteristically do not show tonic extension during an electroshock seizure.[1,2] All animals extend during a spinal cord convulsion; however, flexor cats exhibit extension at a slightly later time than do those animals which characteristically extend in the electroshock seizure.

In addition to the cat, four species (rabbit, rat, hamster, and mouse) have been studied. While each species exhibited characteristic features, all phases of the convulsion shown in Figure 1 were observed in all animals.

The responses of the hindlimbs to stimulation at low frequencies (less than 10/sec.) deserve particular attention. At most stimulus rates the two limbs respond in synchrony to each stimulus. The initial movement is always flexion. At two distinct frequencies (about 3/sec. and 8/sec.) alternating stepping movements, with each limb moving at one-half the stimulus frequency, are observed in the cat. At the higher frequency of stimulation (8/sec.) the stepping movements are superimposed upon weak tonic flexion. These movements, which resemble the natural act of progression, would appear to be similar to those described by Brown,[4,5] who stimulated the cord by transection in a previously decerebrated cat. In Figure 2 such stepping movements are contrasted with the tonic convulsion produced by high-frequency stimulation.

Of especial significance in the record of Figure 2 is the fact that tonic extension

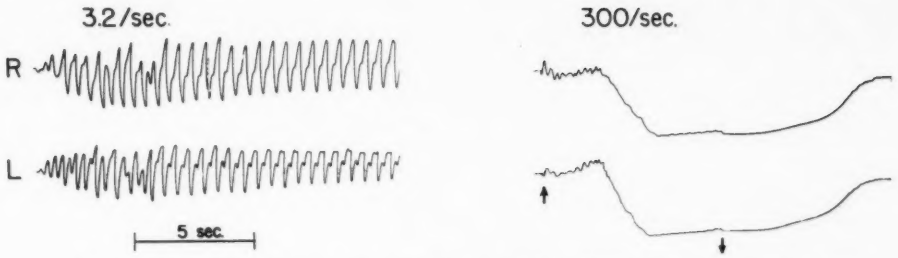

Fig. 2.—Hindlimb responses of cat to spinal cord stimulation, illustrating alternating stepping movements (3.2/sec.) and flexor-extensor convulsion (300/sec.). *R*, right limb; *L*, left limb. Arrows in record at 300/sec. indicate beginning and end of stimulation. The feet of the cat were coupled to strain gauges by means of rubber bands. Flexion is upward and extension is downward in all records. In the record at 3.2/sec. it can be seen that the two limbs are of opposite phase and that each moves at one-half the stimulus rate. The record at 300/sec. shows tonic flexion with superimposed tremor, tonic extension, and persistence of extension beyond the period of stimulation.

continues for about three seconds after the end of stimulation at 300/sec. This indicates that circuits in the spinal cord are capable of producing intense after-discharge. The duration of poststimulation extension as a function of duration of tetanic stimulation of the cord is shown for two species in Figure 3. The negative slopes of the curves indicate that the neurons responsible for the self-sustained activity are themselves fatigued during continued stimulation. With tetanic stimuli too brief to produce tonic extension, after-discharge which produces clonic movements may continue for as long as 10 seconds in the cat. Trimethadione, in an anticonvulsant dose, markedly diminishes the extent of after-discharge in the spinal cord.

The technique of spinal cord stimulation offers a means of assessing, in a rough way, the selectivity of depressant drugs for spinal and supraspinal structures. The anticonvulsant effectiveness of a number of antiepileptic drugs has been compared in cats against maximal electroshock seizures and spinal cord convulsions. These drugs, in order of increasing effectiveness against the spinal cord convulsion, are trimethadione, carbon dioxide, phenobarbital, and diphenylhydantoin. Trimethadione, in minimally neurotoxic doses, has little effect upon the spinal cord convulsion. Diphenylhydantoin,

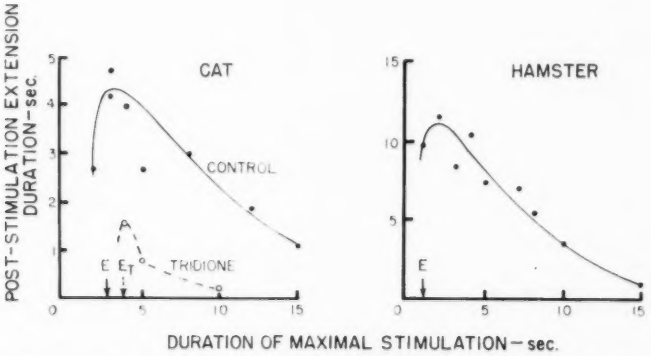

Fig. 3.—Duration of hindlimb extension which persists after stimulation of the spinal cord, as a function of duration of tetanic stimulation in two species. Stimulus frequency was 300/sec. in both instances. Dose of trimethadione (Tridione) was 300 mg/kg., given intravenously. Arrows on abscissas indicate the times of onset of extension in untreated animals (*E*) and following trimethadione (E_T). Note that tonic extension occurs even if stimulation is terminated just prior to the onset of extension.

on the other hand, has a slight effect upon the convulsion in ordinary anticonvulsant doses and a marked effect at the minimally neurotoxic dose. The effect of anticonvulsant medication, as well as that of postictal depression, is to shift upward and to the right the curve dividing the flexor and the extensor field (Fig. 1). Pentobarbital, a general depressant drug, has a profound effect upon the spinal cord seizure in minimally anticonvulsant doses. This indicates a lack of selectivity of this drug for supraspinal structures.

Anticonvulsant drugs, in order to be of clinical value, must affect the origin or spread of epileptic discharge in the brain. Nevertheless, the spinal cord convulsion may be a useful model system, intermediate in complexity between simple reflex arcs and the entire central nervous system, upon which the actions of anticonvulsants and other selective depressant drugs can be investigated.

Comment

With the technique employed, all tracts of the spinal cord, both sensory and motor, are stimulated synchronously. Stimulation of sensory fibers antidromically should have no effect upon the motor response. It would be a remarkable accident, however, if the impulses impinging upon motoneurons of the hindlimb muscles corresponded in temporal and spatial characteristics to those which result from electroshock stimulation of the brain. The problem of simulating the epileptic discharge is not unique to this study but is encountered in all experiments with spinal and supraspinal stimulation. If the motor patterns produced by this technique of stimulation were dissimilar to those observed during a maximal seizure, their interpretation would be difficult. Spinal cord stimulation can, however, faithfully duplicate all the motor responses seen with electroshock stimulation in the intact animal. These experiments suggest, therefore, that the reflex functions of the spinal cord may be of paramount importance in integrating the cerebral discharge into the characteristic motor seizure pattern.

With spinal cord stimulation, purely phasic or purely tonic responses can be predictably obtained by variation in the frequency parameter alone. The response is therefore dependent only upon the number of impulses arriving at the motoneurons in a given time and not upon the origin or function of the tract carrying these impulses.

The voluminous and controversial literature on motor response to stimulation of discrete cortical and subcortical structures is not directly pertinent to the major conclusions to which these experiments point. Such studies (e. g., Rosenblueth and Cannon [6]; Landau [7]; Penfield and Jasper [8]) have shown that tonic and phasic limb movements may be produced by stimulation of a multitude of structures individually. However, during the tonic flexor-extensor convulsion observed whenever the entire brain is maximally stimulated, it can be assumed that there is intense asynchronous activity in virtually all the efferent spinal tracts as a consequence of activity in many cerebral areas. There is little reason to believe that such activity has any functional meaning to reflex systems of the spinal cord; rather, it appears that the stereotyped flexion-extension sequence is the natural response of spinal reflex systems to intense "scrambled" cerebral activity. Inasmuch as the convulsion patterns produced by maximal brain stimulation and by tetanic spinal cord stimulation are identical, it would appear that the latter mode of stimulation effectively duplicates the result of the former. In other words, the spinal reflex systems do not discriminate between the barrages of impulses generated by the two modes of stimulation.

There is correspondence not only between the maximal seizure pattern and that produced by maximal (300/sec.) spinal cord stimulation but also between submaximal generalized seizure activity and the response to low-frequency (less than 50/sec.) spinal cord stimulation. Thus, flexion and the

phasic movements produced by appropriate cord stimulation resemble the flexor and clonic patterns observed following brain stimulation under conditions of central nervous system depression, such as during postictal depression or following anticonvulsant treatment.[1] Similarly, the electroshock seizure patterns described by Millichap[9] in young rats at various stages of development of the nervous system are comparable to the distinct motor patterns (phasic movements, flexion, and flexion followed by extension) produced by successively higher frequencies or spinal cord stimulation.

A surprising and significant finding in these experiments was the appearance in the cat of a pronounced latent phase during high-frequency stimulation. The response to low-frequency stimulation is virtually immediate, indicating brief conduction time in the pathways concerned. During stimulation at 300 per second, however, the flexor phase is preceded by a period of unresponsiveness, lasting approximately 1.5 seconds. A latent phase of similar duration is seen in the cat during the maximal electroshock seizure.[1] While this period in the intact animal may depend in part on the time required for build-up in intensity of the supraspinal discharge, these experiments suggest that the latent phase inherent in the spinal cord may contribute significantly to the total latency in maximal seizures.

In spinal cord preparations which have not been fatigued by excessive stimulation, it is characteristically observed that the response outlasts the period of stimulation. This is true for both the clonic response and the tonic phase of the convulsion (Fig. 2). Thus the spinal cord is capable of intense self-sustained discharge following tetanic stimulation. Although it cannot be questioned that the areas primarily responsible for maintaining seizure discharge in the intact animal are supraspinal, the role of the spinal cord may not be entirely disregarded in this respect. Furthermore, the self-sustained activity of the spinal cord may be generally relevant to the interpretation of studies of the effect of stimulation of supraspinal structures on motor events. Thus, the existence of tonic motor activity following brief stimulation of a region of the brain does not warrant the conclusion that this area produces after-discharge unless supporting evidence, such as electrical records from the site stimulated, is presented.

A striking feature of both the maximal seizure and the spinal cord convulsion is the abrupt change from tonic flexion to tonic extension. The results presented strongly indicate that the determinants of this change in the intact animal are spinal reflex systems. The alternative hypothesis, namely, that the flexor-extensor sequence results from specifically directed suprasegmental discharges, is rendered extremely improbable. An explanation based on the known reflex functions of the spinal cord was proposed in the previous investigation[2]; since it is applicable to the present experiments, it will be briefly restated. The most powerful muscles of the hindlimb are the antigravity muscles, those of physiological extension. Extensor muscles are normally under a considerable degree of background inhibition,[10,11] and this inhibition is enhanced by ongoing interneuronal activity.[12] Thus, the first response of the hindlimb to stimulation is one of flexion (Fig. 2). During sustained flexion, the degree of inhibition of the extensor motoneurons is lessened, with the result that the extensor muscles overpower the flexors. It was shown previously[2] that the change from flexion to extension is dependent upon intact afferent pathways in the lumbosacral cord, and the facilitation of extensor muscles may therefore be presumed to arise from the Golgi tendon organs which are activated during sustained contraction of the flexor muscles.[11] Once the powerful extensors are activated, the limb remains in extension throughout the tonic phase of the convulsion despite continued flexor activity.[2] The terminal clonic movements may depend to a large extent upon interactions between the antagonistic motoneuron pools, through inverse myotatic reflexes,[11] as well as upon the

nature of the seizure discharge which plays upon the motoneurons.

Summary

Continuous, maximal (300/sec.) stimulation of the cervical spinal cord in a decapitate cat results in a sequence of hindlimb movements identical with those seen in the maximal electroshock seizure and in the *grand mal* epileptic convulsion. Thus, the initial latent phase, the brief tonic flexion, and the abrupt change from flexion to extension cannot be ascribed to specific supraspinal events, but appear to represent the natural response of the spinal cord to intense, general stimulation. These motor components have also been observed in four other species of laboratory animals (rabbit, rat, hamster, and mouse).

At low-stimulus frequencies, tonic flexion (10/sec. to 40/sec.) and phasic movements (less than 10/sec.), resembling the manifestations of submaximal generalized seizure activity, can be elicited. Tonic motor activity, once initiated, outlasts the period of stimulation. Thus the spinal cord is capable of intense self-sustained activity, which does not appear to be qualitatively different from that of supraspinal structures.

Clinically useful anticonvulsant drugs have less effect on convulsions produced by spinal cord stimulation than upon seizures elicited by brain stimulation. By contrast, pentobarbital, which is not of value in clinical epilepsy, is equally effective against the two convulsions. The spinal cord convulsion may have utility as a model system in which to investigate loci and mechanism of action of agents and factors which affect abnormal movements.

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Carotid Artery Occlusive Syndrome

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The symptomatology of carotid artery occlusive disease has always been of great interest to clinicians and has been well described in the past.[1-5] It has been emphasized that the patterns and potential course of the disease are numerous and complex. Since the development of therapeutic measures which have been advocated for this condition, it has become essential to study carefully a group of patients with documented carotid occlusive disease. This is particularly so in view of the need for early diagnosis, for the earlier a therapeutic measure is applied the less certain can one be of its effect on the future course of the syndrome. Transient ischemic attacks can occur for a year or more without any residual neurologic deficit being found. In addition, a single stroke may completely resolve without any treatment, and there may be no further difficulty for a few years.

The clinical picture in 57 patients with occlusive carotid disease is presented. The value of the methods of diagnosis presently employed and the possible risks of some are discussed. The variability of the natural history of this syndrome will be described.

Material and Methods

The patients were derived from two separate, but related institutions. From the Stroke Study Files of the Cornell Medical and Neurological Services of Bellevue Hospital, the records of 24 patients with this diagnosis were accumulated in the period 1957-1959. In each patient the diagnosis was confirmed by carotid arteriography. These patients were all personally seen and followed by at least one of us throughout their course after entering the hospital.

From the records of the New York Hospital, 33 patients were obtained in the period 1949-1958. The diagnosis in this group was established by carotid arteriography in 20 patients, by surgical exploration in 5, and by autopsy in 8.

Findings and Comment

1. *Incidence*

It is impossible to make any statements concerning the incidence of occlusive carotid disease in the New York Hospital series, since this was a highly selected group of patients. The 24 patients in the Bellevue group were found in a total of 427 admitted to the cerebrovascular disease study. Arteriograms, however, were obtained in only 84 of these patients.

2. *Age at Time of Diagnosis*

The age at diagnosis ranged from 10 to 87 years, with the maximum incidence at

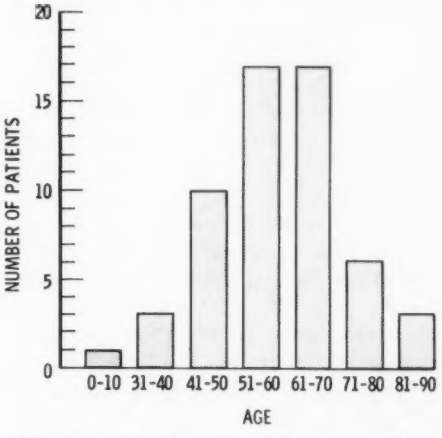

Fig. 1.—Age incidence for all forms of stroke.

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From the Second (Cornell) Medical and Neurological Service, Bellevue Hospital, and the Department of Medicine, the New York Hospital.

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TABLE 1.—*Site of Occlusion of Carotid Artery in Fifty-Seven Patients*

	Right	Left
Unilateral Complete (49)		
Common carotid	0	1
Internal carotid		
Neck	19	21 *
Head	2	2
"Rat-tail" occlusion	3	1
Bilateral Complete (2)		
Neck	2	
Bilateral Incomplete (1)		
Neck	1	
Unilateral Incomplete (5)		
Neck	1	2
Intracranial	--	1
"Rat-tail" occlusion	--	1

51-70 years. The age incidence of the patients was similar to that of the group with all forms of stroke seen at Bellevue Hospital (Fig. 1).

3. *Sex*

There were 39 male and 18 female patients in the combined study. This male predominance is in agreement with the series of other authors.[1-5]

4. *Side and Site of Lesion*

As seen in Table 1, there were 51 patients with a complete occlusion. Forty-one (70%) of the complete unilateral occlusions were localized in the neck. As will be discussed later, the site of the occlusions seems to play some role in the ultimate prognosis. Complete bilateral occlusion occurred in two patients. It is difficult to determine the incidence of bilateral occlusive disease, since only selected patients had bilateral angiography.

5. *Previous Strokes* (defined for the purpose of this communication as a cerebrovascular episode occurring longer than one week before the presenting signs and symptoms leading to the diagnosis of occlusive carotid artery disease)

Fifteen patients (26%) gave a history of a previous stroke from 16 years to 2 weeks before the presenting cerebral incident. Three patients had more than one previous attack (maximum, four). Two patients had involvement on the side opposite that of the demonstrated carotid occlusion.

In 11 patients the history indicated full recovery; in 1 moderate hemiplegia and in 3 some slight degree of aphasia persisted. Aphasia occurred in five patients, and in these aphasia was also a feature of the presenting stroke. Patients with a history of previous strokes did not differ from the series in general in the severity of the presenting stroke or in the prognosis for recovery.

6. *Transient Ischemic Attacks* (defined as episodes with symptoms implicating impairment of the cerebral circulation lasting less than a day and with complete recovery)

Transient ischemic attacks occurred in 22 patients (39%) and were multiple in 15 of these. They occurred from 9 years to 10 days before the presenting stroke. There was no relationship between the number of transient attacks and the duration of time over which they occurred, or the severity of or impairment from the presenting stroke. The symptoms of transient ischemic attacks encountered in this series were visual disturbances, aphasia, alterations in the level of consciousness, hemiparesis, hemisensory defects, and monoparesis. In two patients transient ischemic attacks affected the same side of the body as that of the demonstrated occlusion. Visual disturbances (transient blindness or blurring of vision) were present in 13 patients, usually on many occasions. In three the symptoms occurred in both eyes and suggested possible basilar artery insufficiency.

In two patients a history was obtained of attacks of unconsciousness, lasting a few minutes, months before the presenting stroke. Aphasia occurred in three patients as a symptom of a transient ischemic attack, but only one of these patients had aphasia with the presenting stroke. Hemiparesis, hemihypesthesia, and monoparesis were recorded in eight patients.

The only feature of a history of transient ischemic attacks that is of diagnostic

significance is the occurrence of a repetitive ipsilateral visual disturbance with or without contralateral sensory or motor deficit.[1,6] The appearance of contralateral symptoms makes the diagnosis almost certain. In the present series this symptomatology occurred in 10 patients (18%). However, we have seen this combination of symptoms in a case of glioblastoma multiforme involving the optic tract.

7. Other Symptoms Preceding Diagnosis by Longer Than a Week

(*a*) Epilepsy: In the two patients with epilepsy the seizures were not believed to be due to individual vascular accidents. In one patient, aged 55, focal epileptic seizures began eight years before the admission during which definitive diagnosis was made. In the other, generalized seizures followed a transient stroke 18 months before admission.

(*b*) Headache: Headache has been frequently described as a prodromal complaint, but in five patients headaches were present from five years to six weeks before the presenting stroke. In two patients the cause of the headaches may well have been an intracranial vascular lesion distinct from the carotid occlusion, which was found as an incidental unexpected finding.

The other three patients, however, had symptoms and signs highly suggestive of carotid artery occlusive disease on admission. The headache was bilateral (mainly frontal) in two of these patients, and in the third, although bilateral, it was severer on the side opposite the occluded artery. This latter patient, however, had had a stroke three years previously involving the hemisphere on the side of the uninvolved carotid artery. It is considered likely that in these three patients headache was a symptom of carotid artery disease.

(*c*) Impaired Mentation: Impaired mentation has been frequently mentioned in carotid artery occlusive disease particularly when the disease is bilateral.[2] In two patients impaired mentation preceded the presenting stroke by some months. One patient was 87 years of age, and he lived three years after the stroke, while the other, aged 70, is alive but still impaired intellectually, one year after her stroke.

TABLE 2.—*Prodromal Symptoms*

Impaired mentation	3	
Headache	7	Side of occlusion — 2
		Bilateral — 3
		Side opposite occlusion — 1
		Site unknown — 1
Somnolence	7	
Visual phenomenon	2	
Paresthesia around lips	1	

8. *Prodrome* (defined as a symptom occurring within seven days of the presenting stroke)

One or more prodromal symptoms were present in 14 patients (25%). These are shown in Table 2.

(*a*) Seven patients had headache; in two patients this was the predominant feature, and the diagnosis of intracranial tumor was initially entertained in both cases.

(*b*) Somnolence* was an interesting finding occurring in seven patients. These patients were not confused, as judged by simple tests for orientation and insight. They showed a remarkable propensity for sleep, though easily aroused. The one striking example was a taxi driver, aged 50, who for three days before the onset of aphasia was so drowsy that he fell asleep at the wheel of his cab and, in consequence, had five minor accidents. The relatives and the patient were unaware of any confusion or obvious intellectual deterioration. One can only surmise about the mechanism by which impaired cerebral circulation produces this symptom, but it is reminiscent of hypoglycemic and anoxic states.

9. Onset of Stroke

The mode of onset of the presenting stroke, as shown in Table 3, ran the gamut from marked acute symptoms and signs of disturbance in function to symptoms with no clinical signs at all. In some instances the patients experienced a slowly progressive disturbance of function (13), and in a small number the stroke progressed in step-ladder fashion (2). There was no definite re-

* Carotid—from the greek, *karos*—heavy sleep.

TABLE 3.—*Type of Onset*

	No.
Sudden	33
Slowly progressive	13
Stuttering	2
Investigation of ischemic attacks or old strokes	3
Unexpected finding	5
Unknown	1
Total	57

lationship between the mode of onset and the severity of the presenting findings.

10. *Presumed Etiology*

One cannot be certain as to the etiologic basis for carotid occlusion unless a surgical specimen or postmortem examination is obtained. The presumed diagnoses clinically in the present series are outlined in Table 4. As would be expected, the majority of occlusions were the result of atherosclerosis.

11. *Signs at Diagnosis*

(*a*) Coma: At the onset of the presenting stroke, 13 patients (24%) were comatose. The duration of coma varied from a few minutes to several days, with the individual case.

(*b*) Mentation: Ten patients were found to have impaired mentation at the initial examination. In one patient the mental state was most suggestive of Korsakoff psychosis. Somnolence was noted at the initial examination in three patients, in addition to the seven in whom it was part of the prodrome.

(*c*) Aphasia: Seventeen patients were found to be aphasic, including two in whom it was the primary neurologic finding. All the patients were right-handed; yet one patient had a right carotid occlusion with left hemiplegia. The aphasia in this last patient

TABLE 4.—*Presumed Etiology of Occlusion*

	No.	Per Cent
Atherosclerosis	45	79
Embolism	7	12
"Thromboembolism"	2	4
Arteritis	3	5
Total	57	

was transient, and rapid recovery of motor function was also achieved. Five patients had a history of previous strokes, accompanied by aphasia, and two patients had had previous strokes without aphasia. The severity of the accompanying hemiplegia was variable in degree (from mild to severe). The aphasia persisted throughout the initial period of observation in all but one patient.

(*d*) Motor and Sensory Involvement: Motor and sensory perception dysfunctions were found in 50 patients (88%). In three only reflex changes were evident. In 15 a mild hemiparesis was found. In 9

TABLE 5.—*Signs at Diagnosis in Fifty-Seven Cases*

	No.	Per Cent
Coma	13	23
Impaired mentation	10	18
Aphasia	17	30
Somnolence	9	16
Signs of hemiplegia, hemihypalgesia, and hemianopsia		
(*a*) Reflex changes only	3	
(*b*) Mild	14	86
(*c*) Moderate	9	
(*d*) Severe	23	
Optic atrophy	1	
No signs in nervous system	6*	

* Including five patients in whom occlusion was found incidentally at autopsy or during investigation for symptoms suggesting intracranial vascular anomalies.

patients the hemiparesis was moderately severe, and in 23 it was graded as severe. Sensory perception changes were generally less conspicuous than motor signs. In three patients the sensory changes were severe and involved all modalities of sensory perception. In all patients but one the upper extremity was involved to a greater degree than the lower, and in some patients upper extremity weakness was the only physical finding. This is not surprising, since the area supplied by the anterior cerebral artery is more likely to receive collateral circulation.

(*e*) Horner's Syndrome: Partial Horner's syndrome was found in 6 instances, 5 in the last 13 cases, when we were looking more actively for this sign. The sign was transient in most of the patients and mini-

mal in degree. It was best demonstrated by observing the pupils in a darkened room and after 1% cocaine had been instilled in each eye. This procedure will produce less dilatation on the affected side. The ptosis was more readily observed with the patient looking downward or when awakened from sleep. Only one patient had anhidrosis, and this was not constant. We have also seen a partial Horner syndrome in two persons with a contralateral hemiplegia in whom arteriography was completely normal. Horner's syndrome occurred as the only sign of nervous system dysfunction in one patient.

Comment. In his original description of the syndrome, Horner attributed the sympathetic involvement seen in this condition to pathology in the sheath of the carotid artery. Recent papers in the literature have described the finding of Horner's syndrome in carotid artery occlusion. In one such paper,[7] a partial Horner syndrome was described in 12 of 18 patients, and in 2 patients it was found without occlusion of a major cerebral artery. We believe that this sign is of value in alerting the physician to the possible presence of carotid artery disease in a given patient.

(*f*) Bruits: In 8 of the 24 patients of the Bellevue series, in which bruits were very carefully listened for, murmurs were heard in the neck in 7 and intracranially on the side opposite the occluded carotid in 2 (1 of whom had a cervical murmur on the side of the involved carotid). Two patients in the New York Hospital group were also noted to have a contralateral intracranial bruit, which was reported by Dunning.[8] Fisher [9] has emphasized the importance of a contralateral intracranial bruit in carotid artery disease. A total of four patients (7%) had a bruit in this location.

Bruits in the cervical region are less reliable, for they may merely be indicative of increased flow or an atheromatous plaque within the external carotid artery, without the presence necessarily of concomitant internal carotid disease. We have heard loud systolic bruits, well localized in the cervical region, in patients in whom complete occlusion of the internal carotid was demonstrated.

(*g*) Carotid Artery Palpation: Most authorities agree that palpation of the carotid vessels in the neck is unreliable.[10] Nevertheless, this should be part of every examination, for absence of carotid pulsation in the neck may be significant. Palpation of the internal carotid artery in the pharynx as a diagnostic test was proposed by Dunning.[8] In the present series absence of carotid pulsation in the pharynx was found in 10 of 14 patients having complete occlusion at the bifurcation in the neck. In one patient in whom the carotid pulse was not palpated in the pharynx, arteriography demonstrated good filling of the internal carotid artery. Careful examination and greater skill may result in a higher proportion of positive findings.

(*h*) Retinal Artery Pressures: Ophthalmodynamometry [11] has been found to be highly reliable when the occlusion of the carotid is in the neck. A significantly reduced retinal artery pressure on the side of the occlusion was found in 10 of 13 patients of the Bellevue group (77%). We have recently used this test routinely in all patients with stroke admitted to the Bellevue study and have found that poor cooperation on the part of the patient prevented a satisfactory examination in 10%. Indirect ophthalmoscopy may help to reduce this figure. False-positive results were not encountered. Observation of the vessels of the bulbar conjunctiva has been described recently [12] and may be of value. Paucity of the minute vessels and decreased velocity of the blood flow in all visible vessels of the bulbar conjunctiva have been noted on the side of the occluded carotid.

(*i*) Compression of the Carotid Artery: This was not performed routinely on these patients because this procedure is unpleasant and false-positive results are not infrequent.[13]

(*j*) Miscellaneous: Optic atrophy, associated with a mild contralateral hemiparesis, was found in one patient.

Three patients developed a focal seizure in the first 24 hours of their acute stroke. In two patients the seizures became recurrent.

No signs of altered nervous system function were found in six patients. In one there was bilateral severe stenosis of the carotid arteries, demonstrated by arteriography. This patient had transient ischemic attacks, without any abnormality being found in the neurologic examination. In five of these six patients the diagnosis of carotid artery occlusion was not expected from either the history or the examination. In two the occlusion was found at autopsy; in two during the investigation of headache, and in one following investigation for subarachnoid hemorrhage.

(*k*) Cerebral Spinal Fluid: In 10 patients the protein was greater than 50 mg. %, and in 2 additional patients it was more than 100 mg. %, the highest being 132 mg. %. An elevated cerebral spinal fluid protein is unusual in carotid artery occlusion. When it does occur, it should arouse suspicion of a possible space-occupying lesion, but it is not incompatible with the diagnosis of occlusion.

(*l*) Electroencephalography: In 34 patients electroencephalogram was obtained, and in only 4 instances was normal. The findings were, however, nonspecific, and in one patient the maximal electrical defect was on the side opposite the occlusion. McDowell, Wells, and Ehlers[14] have reported their findings in some of the patients included in this series and have concluded that a useful point in distinguishing this lesion from other lesions, such as neoplasm, has been the relatively normal patterns in the uninvolved hemisphere. Electroencephalographic changes following the use of the tilt table have been described by Meyer et al.[15] Although this modification was not employed on these patients, our experience with 23 patients with basilar artery disease has been disappointing. Electroencephalographic findings with carotid compression suffer from the disadvantages described previously.

(*m*) Surgical Exposure of Carotid Artery in Neck: This has the advantage of avoiding arteriography and giving a clearer picture of the extent of the disease in the neck. The diagnosis was made by this method in five patients.

Comment. The goal of investigators interested in occlusive carotid disease has been to find reliable and simple clinical measures for establishing a diagnosis. It has been the hope of all that angiography might be avoided. This desire is given emphasis by the occurrence of serious complications related to angiography in the present study.[16]

The most reliable measures in our hands have been ophthalmodynamometry and, to a less degree, palpation of the carotid artery in the pharynx. Using all the above-mentioned symptoms, signs, and procedures, exclusive of surgical exposure, the diagnosis of carotid artery occlusive disease can be made at the bedside in a large percentage of patients. Nevertheless, in an appreciable number of patients a diagnosis cannot be made in the absence of angiography or surgical exposure of the vessel.

12. *Course in Hospital and Immediate Prognosis*

(*a*) Deaths: Fourteen patients (25%) died during hospitalization. Two deaths followed valvulotomy for mitral stenosis; one followed internal carotid endarterectomy, and two followed major general surgery. Two patients died of an acute myocardial infarction which had not been suspected prior to death. Four had antemortem pulmonary emboli, which could well have been responsible for death, and three died as a consequence of their carotid occlusions.

It is most interesting that one patient was found to have an asymptomatic old carotid artery occlusion and that no abnormality was observed in the brain at autopsy, death occurring from rheumatic heart disease and multiple emboli.

In the other cases in which autopsies were obtained, lesions, often multiple, were found in the appropriate hemisphere.

(*b*) Recovery: Complete recovery from hemiplegia occurred in all 17 patients (Table 5) whose motor deficit was classified as mild on admission. Of the 32 patients whose motor deficit was classified as moderate or severe, 5 made an excellent recovery (though with residual signs); in 8 a slight recovery was noted, and in 7 no recovery occurred. The remainder of the patients with moderate or severe hemiplegia died.

In 6 of the 10 patients with impaired mentation on admission, the mental symptoms had cleared completely at the end of their period in the hospital.

Of the 17 patients with aphasia, 3 had a complete return of speech at the time of discharge from the hospital. Five of these seventeen patients died during hospitalization, and the remainder were unchanged (including two patients in whom aphasia was the only neurologic deficit at the time of discharge).

Aphasia is the neurologic sign that seems least likely to clear during the acute stroke. The degree of recovery from aphasia could not be correlated with recovery from other neurologic deficits.

13. *Factors Involved in the Immediate Prognosis*

(*a*) Coma: Of the 13 patients seen initially in coma, 6 with persistent coma died during their initial period of hospitalization. The other seven patients were comatose for one hour or less. Three of these experienced a severe hemiplegia; three had a moderately severe hemiparesis, and one had a mild hemiparesis. Five of the survivors subsequently improved appreciably, and the condition of two remained static. If one excludes those patients who died postoperatively and the patient who died of myocardial infarction, it can be seen that marked depression of consciousness of short duration need not be associated with an ultimately poor prognosis, though in all but one patient the accompanying disturbance of function was severe.

(*b*) Site of Occlusion: There was no definite correlation between the ultimate recovery and the side of the lesion except as it affected speech.

Occlusion in the neck can produce any degree of involvement, from none to very severe. Occlusion of the intracranial portion of the carotid artery produced severe physical defects in the five patients in whom it occurred, and these showed, at most, only slight improvement. Progressive narrowing along the course of the internal carotid artery ("rat-tail" defect) produced mild to severe neurologic dysfunction.

(*c*) Bilateral Occlusion: Of the two patients with complete occlusion, one died during the acute phase, and the second patient made an excellent recovery from her stroke. The patient with a complete and a partial occlusion has recovered completely from his hemiplegia, and the patient with bilateral incomplete occlusion has had no functional deficit to date.

(*d*) Heart Disease: Twenty patients of the entire group (35%) had some type of heart disease (Table 6).

All four patients with rheumatic heart disease died, three postoperatively. Two patients with accompanying acute myocardial infarction died in the hospital. Of the four patients with old myocardial infarction, three had mild hemiparesis, and one had a moderate hemiparesis. Of the 10 patients with abnormal electrocardiograms, 6 had severe strokes, 1 a moderate stroke, 3 mild strokes, and 1 no signs of neurologic dysfunction. Two of these patients had auricular fibrillation; both survived—one

TABLE 6.—*Heart Disease*

Type		No. of Patients
Rheumatic heart disease		4
Coronary artery disease		16
Occlusion	6	
Recent	2	
Old	4	
Ischemic	10	
Total		20

with a severe hemiplegia and the other with no neurologic deficit.

(*e*) Hypertension: Twenty-three patients had hypertension (blood pressure greater than 140/90). Hypertension per se did not seem to correlate either with the severity of the stroke or the immediate prognosis.

(*f*) Miscellaneous: Diabetes occurred in five patients in this series and syphilis in one. In none of these was there any evidence of a direct effect on the course of the carotid disease.

It is clear that only prolonged coma and severe cardiac disease are associated with a poor prognosis during the acute attack.

14. *Therapeutic Measures Employed*

Forty patients received no specific treatment. Eleven patients received anticoagulant drugs for longer than four months, and six patients had cervical ganglionectomy performed. No inferences can be drawn about the effect of anticoagulants and cervical ganglionectomy from so small a group of patients. It is of great interest, though, that transient ischemic attacks stopped in each group (Table 7). In five patients who did not receive specific therapy, transient ischemic attacks did not occur after hospitalization or in the follow-up period. However, in two of the five patients the presenting stroke was massive and complete. The follow-up period for the other three was between eight months and one and one-half years.

The three patients treated with cervical ganglionectomy who stopped having transient ischemic attacks were reported previously.[17] The follow-up of these patients has now been extended to two, six, and six years, respectively. Transient ischemic attacks have not recurred over this additional follow-up period.

TABLE 7.—*Therapeutic Measures*

	No Treatment	Cervical Ganglionectomy	Anticoagulant Therapy
No. of cases	40	6	11
Patients with transient ischemic attacks before diagnosis	12	6	4
Ischemic attacks stopped after diagnosis	5	3	3

15. *Follow-Up Observation*

Of the 43 survivors of the acute attack, 5 subsequently died (4 of heart disease). Two patients had a recurrent stroke (one with good recovery), and one patient had a myocardial infarct, with recovery. A follow-up study was not possible in five patients. Of the 30 patients, 3 continue to have rare epileptic seizures. Thirteen of the total group of patients (23%) are now either back at work or able to look after themselves adequately.

Five of the surviving patients (including one with seizures) have some degree of intellectual impairment. The remaining 10 patients have moderate to severe hemiplegia, and 6 have aphasia in addition. Most of these patients are in institutions.

After the presenting stroke, 9 patients survived five years; 20, two years, and 27, one year.

Comment

The striking variability of the clinical picture and prognosis in individual patients with carotid artery occlusive disease is illustrated in Figures 2 and 3. The deleterious effects on the individual patient may vary from minimal to catastrophic; the length of a history indicating cerebral vascular disease may be many years and still be associated with a gainful life. Therefore, any measure advocated in therapy must be a carefully controlled one. The prognosis is serious, and it is in the stroke with acute catastrophic onset that a large percentage of the deaths or severe residual disabilities occurred. In such instances the effects of anticoagulant therapy or surgery on the affected carotid artery are not at present encouraging. A large number of patients must be followed as part of a randomized series by the same group of physicians or surgeons over a lengthy period of time. The excellent work of Millikan et al.,[18]

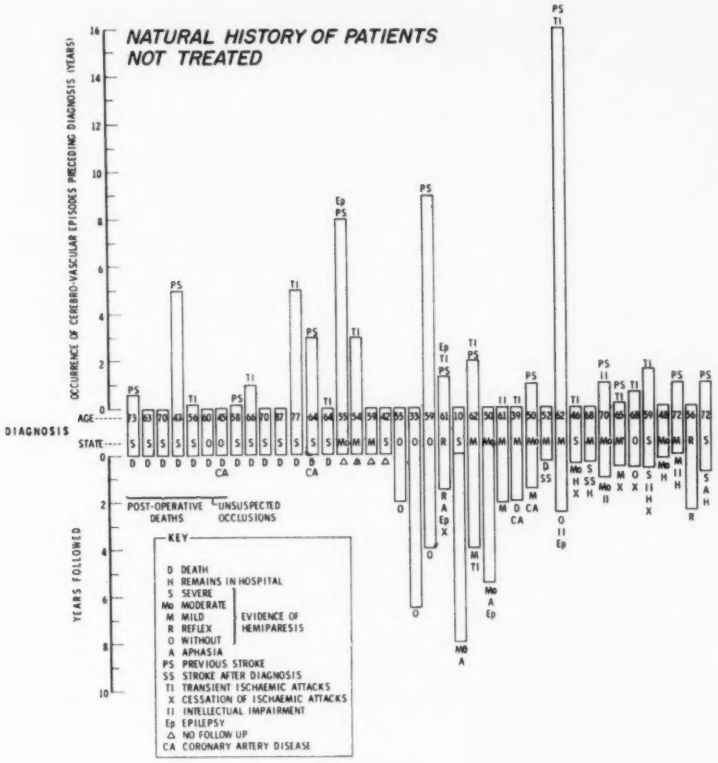

Figure 2

unfortunately, is not based on a controlled randomized series.

In the present series, the general prognosis after the presenting stroke is similar to that described in cerebral thrombosis as a whole,[19,20] and to another series of carotid artery occlusive disease.[21]

More emphasis should be placed on the preceding "minor" cerebral vascular episodes, which are, with the increasing enthusiasm for treatment by both physicians and surgeons, more likely to become the event leading to diagnosis. Of the 57 patients, there are 19 whose first indication of cerebrovascular disease was noted at least five years before the writing of this paper. This gives an opportunity for estimating the natural history of the disease over a five-year period or more from the very first symptom.

Three died within a year; one three years, and three five years, after the first symptom. Three of these deaths were not primarily due to carotid artery disease but were related in time to operative procedures elsewhere in the body; one followed carotid thromboendarterectomy; two followed myocardial infarction, and in only one patient (age 77) was the death directly attributed to the carotid artery occlusion. The other 12 patients are alive from 5 to 18 years after their first symptom.

It becomes evident that in the "natural" state (irrespective of age) survival without symptoms or disability is to be expected for at least a year in most patients with such small "strokes."

Finally, three patients in whom carotid artery occlusion was found unexpectedly may be briefly mentioned. Although we can

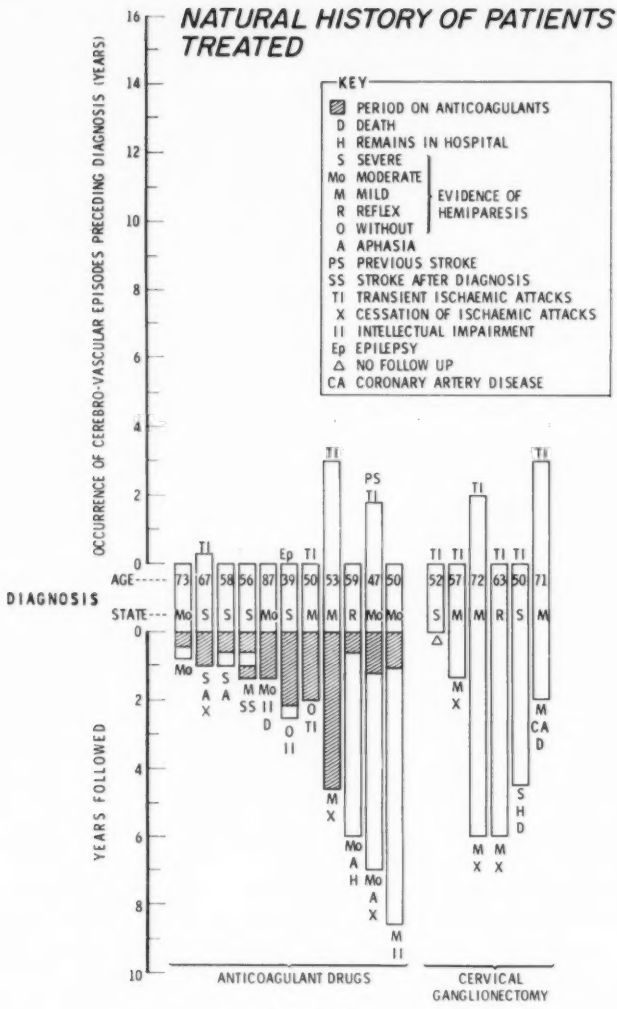

Figure 3

make no comment on their course up to the time of diagnosis, these patients have been followed nine, six, and two years, respectively. None of them has developed signs of hemiplegia and they are fully functional. They were 59, 33, and 55 years of age at the time of diagnosis. These patients seem to answer in part the question posed by Symonds[3] concerning the length of time a spontaneous occlusion may be present without symptoms.

Summary

Fifty-seven patients with demonstrated occlusive disease of the internal carotid artery are described.

A history of a previous stroke was obtained in 15 patients (26%). Transient ischemic attacks occurred in 22 patients (39%) prior to demonstration of the occlusion. Episodic ipsilateral visual disturbance alone or with associated contralateral hemiplegia was described by 10 patients (18%).

Somnolence during the prodromal period occurred in seven patients. The comparative measurements of retinal artery pressure and palpation of the carotid artery in the pharynx were the most reliable bedside diagnostic procedures. Diagnosis without arteriography is considered possible in a majority of instances.

In five patients the transient ischemic attacks ceased spontaneously. Of 19 patients with demonstrable internal carotid artery occlusion, 12 are alive from 5 to 18 years after the first symptom of cerebral ischemia. The majority of these patients had not received any specific treatment. The great variability of the symptoms of intermittent insufficiency and in the life span of these patients emphasizes the need for well-controlled studies of proposed therapeutic measures.

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Alterations of the Alpha Rhythm Occurring After Temporal Lobe Resections in Man

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Introduction

During routine interpretation of electroencephalographic tracings, we observed that postoperative records of patients who had been subjected to temporal lobectomy for control of convulsive seizures consistently showed alterations of the alpha rhythm. Moreover, these alterations did not seem to be directly caused by the surgical procedure per se. They involved areas of the brain which were fairly distant from the region of operation. On occasions they extended to the opposite hemisphere, in some cases being limited to it. The persistence of the alterations for several months, and sometimes even years, argued against their being produced by pathological changes due to surgical trauma.

Searching for possible correlations between changes in alpha rhythm and other clinical and electrical data, we reviewed previous EEG tracings and clinical charts on patients who underwent temporal lobectomies at the University of Minnesota Hospitals during the period from 1954 to 1958. The results of this survey and their relation to other pertinent observations that have appeared in the literature are the subject of the present report.

Material and Method

The clinical records of all the patients who underwent temporal lobectomy between 1954 and 1958 were reviewed. Many cases had to be discarded offhand, owing to lack of specific description of the extent and behavior of alpha rhythm in their preoperative EEG reports, when the original records were not available for examination. An additional number of cases were discarded because their preoperative tracings showed no alpha activity.

Finally, 27 cases were selected. The patients had been subjected to temporal lobectomies, and their preoperative EEG's had repeatedly shown the presence of symmetrical alpha rhythm. Collected data on these patients included pre- and postoperative EEG's, reports of electrocorticography, clinical charts for information about type of seizures, patients' handedness, and postoperative visual field examinations. Pathology reports, with macro- and microscopic description of the operative specimens, were also reviewed. Some patients who did not have satisfactory postoperative EEG follow-up were recalled and new records were taken. Unfortunately, not all of these patients were available, and therefore our data for some of them are not complete.

Both bipolar and "monopolar" techniques were used for the electroencephalograms in all cases. The majority of tracings were recorded with 20 electrodes arranged according to the "10-20" system. The older tracings were recorded with 14 electrodes placed symmetrically in frontal, central, parietal, occipital, and anterior and posterior temporal areas, and in the ear lobes.

Results of pre- and postoperative audiologic and psychological examinations will be reported elsewhere, together with the rest of the clinical information and detailed histological descriptions.

Our group included 21 males and 6 females. The youngest patient was 10 years of age and the oldest 53. Ten patients were in the second decade of life; six, in the third; five, in the fourth; four, in the fifth, and two, in the sixth. All the patients had had temporal lobe epilepsy prior to surgery.

In order to secure a control group of patients, we looked through the cases which had extratemporal cortical resections or temporal gyrectomies for control of epilepsy. After discarding the cases with space-occupying lesions or vascular

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malformations, and also those which had insufficient data and in which no further information could be obtained at the time of the investigation, we ended with only four cases which were considered suitable as controls. This group included three women and one man. Their ages were 18, 25, 23, and 27, respectively. One had a superior temporal gyrectomy; one had a posterior parietal and superior temporal cortical resection; one had a right postcentral gyrectomy, and one had a bilateral parasagittal frontal gyrectomy.

The temporal lobectomy patients presented variable distribution of alpha rhythm in their preoperative records. In 14 patients this rhythm extended over parietal, posterior temporal, and occipital areas; in 8 it included, in addition, the frontal and anterior temporal leads. In two patients the central leads, in addition to the parietal, posterior temporal, and occipital areas, showed alpha activity, and in two patients the alpha rhythm was limited to the parietal and occipital areas. In one patient the description of the record only gave a basic frequency in the alpha range but did not give the distribution of it. The original tracings were not available.

Two of the control patients presented parietal, posterior temporal, and occipital alpha distribution. In one this rhythm extended in addition to the central areas, and in one more it was limited to posterior temporal and occipital leads.

All the records had abnormal background activity, which varied in degree. All the patients in the temporal lobe group had also focal abnormalities in one or both temporal lobes.

None of our patients had tumors or vascular malformations. The pathological study of the specimens removed disclosed either normal cerebral tissue or some degenerative or atrophic changes.

Results

The patients were classified in three groups according to the degree of alteration of alpha rhythm after the operation, and a fourth group comprised controls.

GROUP I.—Seven patients had insignificant amounts of or no alpha rhythm at all in one or both hemispheres at the time of their last postoperative EEG (Fig. 1). The follow-up period after the operation varied from one month to three years. These patients were all right-handed. Five had a right temporal lobectomy, and two had a left temporal lobectomy. Extent of lobectomy was 9 cm. from temporal tip to posterior margin of excision in three cases, 7 cm. in three cases, and 5 cm. in one case. Three patients had a homonymous hemianopsia after the operation; one could not be tested for visual defect, and the other three had homonymous quadrantic defects (Table 1).

GROUP II.—Five patients presented no asymmetries or other significant changes of their alpha rhythm in postoperative records (Fig. 2). Their follow-up periods ranged from 9 to 16 months. Three of these patients were right-handed. Handedness was not known in the other two. Three patients presented a homonymous quadrantic defect. No visual examination could be obtained in the other two patients. There were three right-sided and two left-sided temporal lobectomies in this group. The area resected was 5 cm. long in one patient, 5.5 cm in its upper border and 6 cm. in its lower border in another, and 6.5, 7, and 11 cm. long in the other three patients (Table 2).

GROUP III.—Fifteen patients showed either only transitory alterations of their

Fig. 1.—Comparison of pre- and postoperative tracings of Patient I 7 (Group I). Note complete absence of alpha rhythm on EEG taken more than three years after right temporal lobectomy. Date of operation: March 10, 1955. Calibration: 50μv.; 1 second.

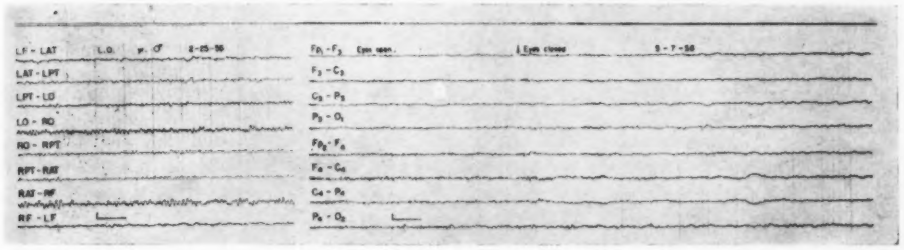

TABLE 1.—*Cases Presenting Uni- or Bilateral Absence of Alpha Rhythm After Temporal Lobectomy (Group I)*

Name	Preoperative Alpha		Handedness	Type of Temporal Resection	Extension of Area Resected, Cm.	Postop. Visual Field	Postop. Alpha
	Freq.	Distrib.					
I 1	10/sec.	Parietal, occip., posterior temp.	Right	Left lobectomy, including uncus and hippocampal gyrus	9	Right homonymous hemianopsia	2½ mo. postop.: Absent in left hemisphere
I 2	10/sec.	Parietal, occip.	Right	Right lobectomy	9	Left homonymous hemianopsia	2 yr. postop.: Absent in right hemisphere
I 3	9-10/sec.	Parietal, occip., posterior temp.	Right	Right lobectomy	7	Left homonymous superior quadranopsia	3 yr. postop.: Absent bilaterally except for right occip.
I 4	7-8/sec.	Parietal, occip., posterior temp.	Right	Left lobectomy	9	Right homonymous hemianopsia	7 mo. postop.: Practically absent bilaterally
I 5	9/sec.	Partial occip., posterior temp.	Right	Right lobectomy	7	?	1 mo. postop.: Practically absent bilaterally
I 6	9-10/sec.	All areas	Right	Right middle and inferior gyri removed *	7	Left homonymous superior quadranopsia	2 yr. postop.: Absent bilaterally except for small amount in left occiput
I 7	9-10/sec.	All areas	Right	Right lobectomy, including uncus and amygdala	5	Left homonymous superior quadranopsia	32 mo. postop.: Only occas. runs of 8 sec. in right central area

* This patient developed a postoperative abscess in the right temporal region. It had to be evacuated.

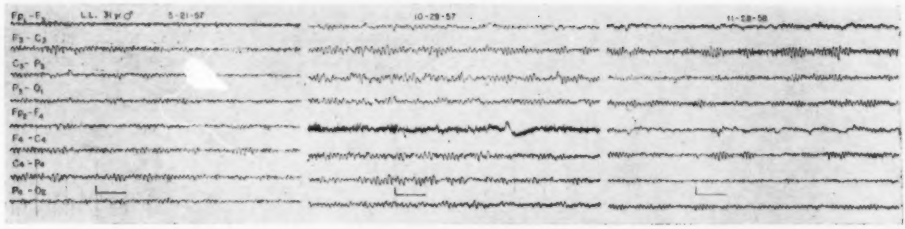

Fig. 2.—Pre- and postoperative records of Patient II 3 (Group II). No significant alteration of alpha rhythm after left temporal lobectomy. Date of operation: Oct. 14, 1957. Calibration: 50μv.; 1 second.

alpha rhythm or a more durable asymmetry, but no absence of this rhythm on either side (Fig. 3). The follow-up period was only 16 days in one case. It varied from 3 to 30 months in 13 cases, and it went up to 4 years 10 months in 1 case. Twelve patients in this group were right-handed; one was left-handed, and in two more it was not possible to obtain information about handedness. Nine of these patients had a left temporal lobectomy, and six had a right-sided resection. Extension of the area resected varied in the largest dimension from 5 to 8 cm. In one patient the resection extended over 7 cm. in its superior border and 10.5 in the inferior border. Ten patients in this group had a homonymous quadrantic defect. Four were not tested for visual defects, and only one had a homonymous hemianopsia. This was, however, of the incongruous type. It was present in a patient who had only 5 cm. of his left temporal lobe resected (Table 3).

GROUP IV.—All four controls with extra-temporal or temporal gyral resections had alterations in the alpha rhythm after operation, but in none was this rhythm absent on either side. Their follow-up periods ranged from 11 to 27 months (Table 4).

Seven patients of the temporal lobectomy group showed typical *Arceau* rhythm [7] after operation. This rhythm appeared only on the side of the temporal resection in six patients and bilaterally in one. *Arceau* rhythm was not present in any of the controls (Group IV).

Bilateral temporal spikes were present in preoperative tracings in only two cases. These two patients belong to Group III and showed asymmetric alpha activity after operation. In addition to these two cases, there were five postoperative records presenting spikes recorded from the temporal area opposite the side of the operation. This abnormality was seen only after surgery in these patients. Of these five patients, one had practically no alpha activity (I 4, Table 1), one showed no changes in alpha rhythm (II 1, Table 2), and three showed asymmetries in alpha rhythm (III 6, III 14, III 12, Table 3) and belong to Group III.

Spikes persisted or appeared postoperatively in the temporal area on the side of the operation in 12 patients. Five of these showed absence of alpha rhythm on one or both hemispheres and are included, therefore, in Group I. One showed no alteration in alpha activity after operation (Group II), and six showed only asymmetry; alpha rhythm was, however, present bilaterally (Group III).

As mentioned before, detailed evaluation of clinical status and other special tests will be the subject of separate communications. It may be of interest, however, to mention briefly the follow-up of seizure frequency postoperatively in our three groups of patients.

Of the whole group, only three patients did not show any significant improvement in seizure frequency. One of these presented, in addition, a psychotic episode. These three patients were in Subgroups II and III of our group. Seven patients showed significant improvement in seizure frequency

TABLE 2.—*Cases with No Alterations of Alpha Rhythm After Temporal Lobectomy (Group II)*

Name	Preoperative Alpha		Handedness	Type of Temporal Resection	Extension of Area Resected, Cm.	Postop. Visual Field	Postop. Alpha
	Freq.	Distrib.					
II 1	10-12/sec.	Parietal, occip., posterior temp.	?	Right lobectomy	5.5-6	Left homonymous superior quadranopsia	14 mo. postop.: 10/sec.; symmetrical
II 2	8-10/sec.	All areas	Right	Right lobectomy	7	Left homonymous superior quadranopsia	13 mo. postop.: 8-12/sec.; symmetrical
II 3	8-9/sec.	All areas	Right	Left lobectomy	6.5	Right homonymous superior quadranopsia	14 days 1 yr. postop.: 8-9/sec.; symmetrical
II 4	10/sec.	Parietal, occip., posterior temp.	Right	Left lobectomy	11	?	16 mo. postop.: 9-10/sec.; symmetrical
II 5	9/sec.	?	?	Right lobectomy	5	?	9 mo. postop.: 9-10/sec.; symmetrical

but still had occasional episodes in spite of anticonvulsant medication. One of these belongs to Subgroup I because his EEG showed marked alterations of the alpha rhythm. The others belong to Subgroups II and III. Four of these patients in Subgroups II and III had to be committed to mental institutions for severe behavior disorders.

The rest of our patients presented no seizures, or only occasional minor spells after operation. Our Subgroup I, with the severest alterations in alpha activity, is thus formed by patients who had the best results, except for one, mentioned above, who still has seizures but shows improvement from the preoperative condition.

Comment

Alterations of the alpha rhythm in the presence of cortical lesions have been observed by several authors. Case[2] reported substantial difference between the occipital alpha waves on the two sides in cases with lesions involving the optic radiations. His series included space-occupying lesions in parietal, occipital, and temporal lobes, and also an intraventricular meningioma. All these patients presented more or less extensive visual field defects, and all had alterations of the alpha rhythm on the side of the lesion. From this, the author concluded that the geniculocalcarine pathway was at least part of the anatomical structure responsible for the production of alpha rhythm.

Williams and Reynell[23] analyzed a series of cases with penetrating gunshot wounds and compared them with normals and with close head injuries. They concluded that the most important factor for abnormal suppression of alpha rhythm was not the extent of the lesion but its location. Lesions in the parieto-occipital cortex produced extensive suppression of alpha activity in the affected hemisphere, whereas frontal, temporal, or occipital lesions produced either no change in this activity or only local suppression of it. Although in some of

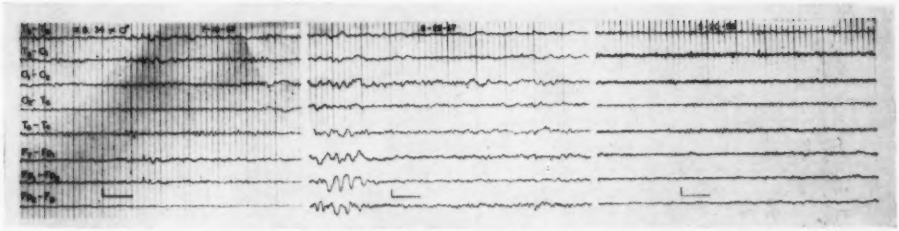

Fig. 3.—Pre- and postoperative records of Patient III 2 (Group III). Only mild transitory asymmetry of alpha activity after left temporal lobectomy. Date of operation: Aug. 21, 1957. Calibration: 50μv.; 1 second.

their cases there was a coincidence of absence of alpha rhythm and involvement of the visual pathways, they attributed this to anatomical proximity and denied a direct influence of the geniculocalcarine fibers on the alpha rhythm. They supported their belief with cases that had relatively small lesions in occipital or temporal areas which gave marked impairment of visual field but only local changes in alpha activity.

Suppression of alpha activity may follow disturbances of parieto-occipital cortex according to Courville,[3] who agrees in this point with Williams and Reynell.[23] In addition, midline cerebellar tumors and bilateral occipital lesions may also produce suppression of this activity (Courville[8]). In contrast with investigators who think of the parieto-occipital cortex as the pacemaker for normal activity of the EEG, as do Williams and Reynell[23] and Courville,[3] and with Case,[2] who thinks that the optic radiations are essential for the production of normal alpha rhythm, Masland and Austin[14] believe that the temporal lobe is capable of generating alpha rhythm. They found overactivity of one temporal lobe both in abnormal activity and in alpha rhythm after occipital lobectomy of the same side.

Some new developments concerning the alpha rhythm have their origin in experiments of Morison and Dempsey[16] and Dempsey and Morison.[4] These authors described for the first time a system in the intralaminar nuclei of the thalamus which, when stimulated at appropriate frequencies, produces a typical "recruiting response" in the cortex. Rose and Woolsey[19] proposed the reticular thalamic nuclei as a distributing system for the diffuse projection of the intralaminar nuclei. Jasper,[9] a few years later, demonstrated rhythmic waves recorded from the cortex in response to single stimuli applied to the thalamic reticular system. He emphasized that in form and frequency the induced "bursts," made up of 8- to 12-per-second waves, are almost undistinguishable from those which occur spontaneously, and that these rhythmic waves are, therefore, most likely analogous to the alpha rhythm of the human EEG. All these findings, supplementing each other, point toward a centrally located pacemaker for the alpha rhythm.

There is, on the other hand, evidence in favor of spontaneous rhythmic activity produced by neuronally isolated cerebral cortex.[5,13,20] Furthermore, with simultaneous cortical and subcortical recordings, rhythmic activity can be detected from both the cortex and the thalamus. The rhythm in the two areas is, however, not synchronous, although the frequency is maintained in the same range.[21] In recent years strong evidence has been found pointing to cortical dendritic potentials as important constituents of alpha activity.[1,8,18]

In spite of the evidence in favor of the existence of "spontaneous" activity of the cerebral cortex, there is no doubt that midline, deeply located structures are able to exert control upon the cortical rhythms; the brain-stem reticular system produces dysynchronization, and the thalamic diffuse

TABLE 3.—*Cases with Partial or Temporary Changes in Alpha Rhythm After Temporal Lobectomy (Group 3)*

Name	Preoperative Alpha		Handedness	Type of Temporal Resection	Extension of Area Resected, Cm.	Postop. Visual Fields	Postop. Alpha	
	Freq.	Distrib.					First Follow-Up	Last Follow-Up
III 1	10-11/sec.	Central, posterior temp., occipital	Right	Right lobectomy	6	?	10 days postop.: 9/sec.; left higher, clearer than right	7 mo. postop.: 10/sec.; symmetrical
III 2	7-9/sec.	Posterior areas	Right	Left lobectomy, including uncus and hippocampal gyrus	6	Right homonymous superior quadranopsia	8 days postop.: Small amt. 9/sec. in central areas	9 mo. postop.: Symmetrical
III 3	10/sec.	Parietal, post. temp., occipital	Right	Right lobectomy, including uncus-hippocampal gyrus	7 above; 10.5 below	Left homonymous superior quadranopsia	22 days postop.: 9-10/sec., higher on left	3 mo. postop.: Asymmetrical, higher on left
III 4	8-9/sec.	Parietal, post. temp., occipital	Right	Left lobectomy, including hippocampal gyrus	7	Right homonymous superior quandranopsia	10 days postop.: 8/sec.; absent on left	3 mo. postop.: 9-10/sec.; higher on right
III 5	8-10/sec.	Posterior areas	Right	Left lobectomy	8	Right homonymous superior quadranopsia	3 wk. postop.: 9/sec.; higher voltage on right	10 mo. postop.: 9-10/ higher voltage on right
III 6	9/sec.	Parietal, post. temp., occipital	Left	Left lobectomy, including uncus-hippocampal gyrus	5	Right homonymous hemianopsia (incongruous)	20 days postop.: 8/sec.; practically absent on left	12 mo. postop.: 7-8/sec.; higher on right
III 7	8-11/sec.	All areas	Right	Left lobectomy, including uncus and part of hippocampal gyrus	5 above; 7 below	?	16 mo. postop.: 8-9/sec.; higher voltage on left	30 mo. postop.: 8-9/sec.; symmetrical
III 8	10-11/sec.	Parietal, occipital, posterior temp.	?	Right lobectomy, including uncus and hippocampus	6	?	7 days postop.: 10/sec.; decreased voltage on right	14 mo. postop.: 10-11/sec.; no asymmetry
III 9	9-10/sec. (Ill defined)	Parietal, occipital, posterior temp.	?	Left lobectomy, including amygdala	6	Right homonymous superior quadranopsia	6 wk. postop.: 10-11/sec. (ill def.); higher voltage on left	5½ mo. postop.: 8-12/sec.; more alpha activity on left
III 10	8-9/sec.	Posterior areas	Right	Right lobectomy	6	Left homonymous superior quadranopsia		2 yr. postop.: 9/sec.; higher voltage on left

III	11	10/sec.	Parietal, occipital, posterior temp.	Right	Left lobectomy	7	Partial right homonymous superior quadranopsia	16 days postop.: 10/sec.; better organized, higher voltage on left	
III	12	8-9/sec.	All areas	Right	Left lobectomy	4	?	9 mo. postop.: 8-9/sec. (ill defined); voltage higher on left	
III	13	9/sec.	Posterior areas	Right	Right lobectomy 2×3 cm. of frontal operculum	7 2×3	Left homonymous superior quadranopsia	13 days postop.: 10/sec.; bilateral, higher on left	9 mo. postop.: 9-10/sec.; no asymmetry
III	14	10/sec.	Posterior areas	Right	Left lobectomy	7	Right homonymous superior quadranopsia	18 days postop.: 10/sec.; right; no alpha on left	13 mo. postop.: 8-10/sec.; bilaterally voltage higher on left
III	15	8/sec.	All areas	Right	Right lobectomy	8	Left homonymous superior; defect extending slightly more than the superior quadrant	2 mo. postop.: 9/sec.; voltage higher on left	5 yr. postop.: 9-10/sec. in left posterior area and in right occiput

TABLE 4.—*Temporal Gyrectomies and Extratemporal Cortical Resections (Group IV)*

	Preoperative Alpha				Extension of Area		
Name	Freq.	Distrib.	Handedness	Type of Temporal Resection	Resected	Postop. Visual Field	Postop. Alpha
IV 1	9-10/sec.	Parietal, occip., posterior temp.	?	Right superior temporal gyrectomy	Gyrus 6 cm. long	?	27 mo. postop.: Small amount posteriorly bilaterally
IV 2	10/sec.	Posterior temp., occipital	Right	Bifrontal parasagittal gyrectomy		?	15 mo. postop.: Small amount in occiput bilaterally
IV 3	9-10/sec.	Posterior temp., occipital, parietal	Left	Left posterior parietal-temporal resection		Normal	11 mo. postop.: Small amount posteriorly, more on right
IV 4	7-9/sec.	Central, parietal, occipital	?	Right postcentral gyrectomy		?	2 yr. postop.: Asymmetry Left voltage higher than right

projection system produces rhythmic spindles in the cortex.

Corticifugal projections to the reticular system have been demonstrated from many cortical areas,[6,10] and it is, therefore, not unlikely that the cortex has also an important influence over the diffuse projection system of the thalamus and brain stem. Moreover, limited regions of the cortex have also influence upon the electrical activity of large cortical areas. This influence is probably exerted via corticothalamocortical pathways.[17] Morison, Dempsey, and Morison [15] found that temporal lobe lesions in the cat abolished not only the "secondary response" to peripheral sensory stimulation but also the spontaneous activity of part of the affected hemisphere.

Our cases indicate that the alpha rhythm may suffer alterations not only from temporal resections but also from extirpation of other cortical areas. All our controls presented more or less long-lasting postoperative changes in their alpha rhythm.

Analysis of the cases with temporal lobectomy reveals a few outstanding facts. All the patients whose visual fields were tested showed a homonymous defect. The extension of this field defect was, in general, larger in patients included in Group I (Table 1). In fact, the only cases with hemianopsia were found in this group. The only exception to this statement is I. G. in Group III (Table 3), who also presented a hemianopsia. The defect in this patient was, however, incongruous, and it is therefore reasonable to assume that factors other than the temporal resection may have been the cause of it. There may be a lesion in the optic tract. Incongruous homonymous field defects are typically produced by lesions in this part of the optic pathway.

The second outstanding fact is a significant difference between the extension of area resected in Group I and that resected in Group III. No significant difference was found between Groups I and II. The latter group is very small, however, and the difference would have to be rather large in order to be statistically significant.

TABLE 5.—*Postoperative Temporal Spikes on the Side of Lobectomy*

	Cases With Spikes	Cases Without Spikes	Total
Group I	5	2	7
Group III	6	11	15
Total	11	13	22
		$\chi^2=1.3$	

We use the t-test $T=\frac{\text{Difference of means}}{\text{Standard error of difference}}$ to evaluate the significance of differences. The result for ^{t}Group I, Group II, is 0.4, which is not significant in the presence of 10 degrees of freedom ($P=0.1$); ^{t}Group I, Group III was 2.2, which is significant for 20 degrees of freedom ($P=0.05$).

The third fact that is of possible interest in our series is the distribution of cases, which presented a spike either residual or new in the temporal area on the side operated upon (Table 5). No statistically significant difference was found when we calculated χ^2 for Group I (spikes in 5 cases out of 7, or 71%) and Group III (spikes in 6 cases out of 15, or 40%). The higher percentage of spikes in Group I is, however, suggestive. The opposite is found for the incidence of spikes on the side contralateral to the temporal lobectomy for this group (Table 6).

In view of the relationship of alpha rhythm to consciousness, and probably also to mental processes, and in the presence of psychological and memory disturbances reported in cases of temporal lobectomy,[11,12,22] it is tempting to associate the

TABLE 6.—*Postoperative Temporal Spikes on the Side Opposite the Lobectomy*

	Cases With Spikes	Cases Without Spikes	Total
Group I	1	6	7
Group III	5	10	15
Total	6	16	22
		$\chi^2=0.1$	

temporal lobe with alpha mechanisms. In the presence of our results, however, we find no good evidence for assigning a specific direct relationship between temporal lobe and production of alpha activity. We found alterations of alpha rhythm in patients who had cortical resections in frontal and parietal areas, and other authors have reported the same findings. Although experimental results mentioned above [17] may indicate a great influence of temporal cortex on alpha activity, we do not believe that this is the only cortical area which influences this activity.

We agree with Williams and Reynell [23] when they say that involvement of geniculocalcarine pathways is not essential for abolition of alpha activity. Our evidence to support this belief is not as strong as that presented by the above-mentioned authors. However, of our patients who presented no postoperative changes in alpha activity, the only three who had visual field tests had a field defect (Table 2). We feel that in our series the presence of homonymous hemianopsia merely reflected a more extensive involvement of temporal tissue. This is substantiated by the significant difference in amount of removed tissue between Groups I and III.

It is probable that when large enough portions of cortical tissue are resected from practically any area in the brain, permanent alterations of the alpha rhythm may appear. As has been suggested on other occasions,[22] it is also possible that the presence of a spike discharge might increase the area of dysfunction of the temporal lobe. We find, therefore, of possible interest the higher incidence of postoperative spikes in the temporal area on the side of operation in the group of patients who had the severest alterations of alpha activity. The dysfunction may be increased by the presence of this abnormal discharge, giving results equivalent to a more extensive resection.

Corticothalamocortical connections involving the diffuse projection system are probably the mediators of abnormal suppression of alpha rhythm produced by cortical resections.

The higher number of good clinical results in our Subgroup I, although not important enough to be statistically significant, is somewhat intriguing. It would suggest that good clinical results have a direct relationship with degree of alteration of alpha rhythm after surgery. Any discussion of this possibility at this point, however, would be based on pure speculation and should be postponed until enough data are collected for it to be statistically important.

Finally, it should be emphasized that our results were obtained in patients with convulsive disorders and diffuse alterations in their electroencephalogram. Caution should, therefore, be used when these findings are applied to interpretation of normal physiological phenomena.

Summary

Pre- and postoperative EEG's of 27 patients who underwent temporal lobectomy for control of convulsions were studied. All these patients showed clear and symmetrical alpha rhythm before surgery. Extension of surgical resection, as well as amount of postoperative visual field involvement, was noted. Residual or new abnormalities appearing after the operation were also evaluated.

Four cases subjected to limited temporal gyrectomies or to cortical resections not involving the temporal lobe were studied in a similar way and served as controls.

Of the 27 patients with temporal lobectomy, 7 showed absence of alpha rhythm in one or both hemispheres after surgery. The follow-up period ranged from one month to three years. Fifteen patients of the same group showed either transitory alteration of the alpha rhythm or a more persistent asymmetry but no absence of this rhythm. The rest (five patients) presented no alterations in their alpha rhythm after operation.

All four control cases showed postoperative alterations of their alpha rhythm, but none showed absence of it on either side.

Significant correlation was found between extension of area resected, degree of visual field defect, and severity of alteration of the alpha rhythm after operation. Possible correlation was also found between the latter factor and presence of postoperative spikes on the side of the operation.

Other factors encountered, as well as possible mechanisms for changes of alpha rhythm after resections of brain tissue, are discussed. It is concluded that resection of almost any cortical area may cause abnormal and extensive suppression of alpha rhythm, and that the amount of cerebral tissue resected is more important than the site of the resection for suppression of normal electrical activity.

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Antihistamines in Treatment of Gingival Hyperplasia Caused by Diphenylhydantoin

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Since its introduction by Merritt and Putnam in 1938,[1] diphenylhydantoin (Dilantin) sodium has become one of the most widely used anticonvulsants. Although it is relatively nontoxic, gingival hyperplasia occurs in up to 50% of patients.[2,3] In most instances, proper oral hygiene effectively controls the gingival reaction. In a small number, possibly 2% or 3%, the hyperplasia may become sufficiently prominent to require some modification of dosage or gingivectomy. Not infrequently, it is impossible to find another drug or combination of drugs which has as good an anticonvulsant effect. Since no effective means of preventing or treating the severe reactions has appeared, they may remain therapeutic problems.

Our interest in this phenomenon was stimulated by a clinical report (Gaillard[4]) suggesting that gingival hyperplasia can be modified by the antihistamine chlorprophenpyridamine maleate (Teldrin Spansules). After initiating a clinical study, we were further encouraged by the work recently reported by Francis,[5] in which histamine mechanisms are implicated.

Two groups of patients were studied. The first included 13 patients. These were graded as having mild (Grade 1), moderate (Grade 2), or severe (Grade 3) hyperplasia. In Grade 1 were placed those patients who had pegs of hyperplastic tissue between their teeth. In Grade 2 were placed patients with crescentic ridging and definite impingement upon the clinical crowns of the teeth but with less than half of any one tooth covered. Grade 3 patients had severe overgrowth covering most of their teeth and large, irregular masses of tissue growing away from them. There was a varying degree of hyperemia and bleeding, which was more prominent in the severely involved gums.

These patients were then given an antihistamine and examined at monthly intervals. Our earliest cases were given diphenhydramine (Benadryl) HCl since chlorprophenpyridamine was not available. The dosage of the former was 10 to 50 mg. three times each day. Later, Teldrin sustained-release capsules, containing 8 to 12 mg. of chlorprophenpyridamine, was given twice each day to another group of patients.

In the diphenhydramine group there were five patients. In four the hyperplasia was classified as Grade 2 and in one as Grade 3. All but one of these patients reported slight improvement in that there was slightly less bleeding and minimal recession of gingival tissue. On examination, no definite change was seen in two patients, but in the others the gums seemed to have receded slightly.

In the chlorprophenpyridamine-treated group, there were eight patients. Two were in Grade 1, five in Grade 2, and one in Grade 3. Very little subjective or objective change was noted in the Grade 1 patients, though the gums did appear slightly paler. Of the patients with moderately severe hyperplasia, two had previously been given diphenhydramine. Both reported more definite improvement on chlorprophenpyridamine therapy. However, there was no

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further change in the appearance of the gums. Finally, the remaining four patients, with moderately or severely involved gums, reported complete relief of soreness of gums in three cases and a marked decrease in bleeding and distinct recession of gingival tissue in all. On examination, the gingivae appeared paler, firmer, and less friable. There did seem to be some recession of tissue, though not sufficient to change the grade in which the patients were placed.

We were impressed by the fact that those patients who complained of sore gums or excessive bleeding had improved significantly. The gums which were friable and erythematous became firmer and paler in color. The hyperplasia itself did not seem to change except in the severer cases, in which there did seem to be some measurable recession of gingival tissue. On the other hand, we had by this time observed the extension of hyperplasia in two patients who were given diphenylhydantoin while taking an antihistamine.

Because of the difficulty of making an objective evaluation, a second group, of 11 patients with varying grades of hyperplasia, was located at the Vermont State Hospital. These patients were all adults who had been taking diphenylhydantoin for many years. A double-blind experiment was set up in which six patients were given 24 mg. of sustained-release chlorprophenhydramine divided into two or three doses daily for two months. Five patients were given an identical-appearing placebo. All patients were examined immediately before institution of therapy and on the last day of therapy. These examinations included color and black-and-white photography and gum biopsy. Most patients were unable to report subjective changes reliably.

Of the six chlorprophenpyridamine-treated patients, one was in Grade 3, and it was felt that his gums were somewhat paler and firmer. However, this could not be confirmed on analysis of the pictures, nor did the biopsy reveal any significant change in the hyperplasia. Two of the patients were in Grade 2, and in one instance there was felt to be slight changes on observation, which could not be confirmed by the photographs. In the remaining three patients, all in Grade 1, no significant changes were seen in the photographs or in the biopsy tissues. No significant changes were noted in any of the placebo-treated group.

As part of the blind analysis of both the photographs and the biopsy tissue, an attempt was made to select the pre- and post-treatment representations, without success. There seemed to be some fluctuation of color in each group. There was also some fluctuation in the inflammatory element in the biopsy specimens of both the treated and the untreated patients. There was no change in the hyperplasia in any case.

During this study, five additional patients were subject to a similar analysis except that all received cholorprophenpyridamine. In these patients, too, an observer who was unfamiliar with the plan of the study was unable to select the pre- and post-treatment photographs and biopsy tissue.

The exact nature of the gingival hyperplasia induced by diphenylhydantoin is not known. Though poor oral hygiene and other local factors aggravate this phenomenon, most workers agree that the hyperplasia itself is drug induced. Clearly, it is not due to ascorbic acid (vitamin C) deficiency, as was originally proposed.[6] In a preliminary report, Staple demonstrated adrenal hyperplasia, as well as gum hyperplasia, in ferrets[7] given diphenylhydantoin. This led him to speculate that the gum hyperplasia might be associated with deranged adrenal function. More recently, Francis and Melville[5] presented evidence to show that the hyperplastic gums of ferrets contain an excess of extractable histamine. This, he feels, is evidence of an allergic mechanism, as has been proposed by several investigators.[8]

On the basis of this study, we feel that there is no evidence to support either a relationship of histamine to gum hyperplasia or a reversal of diphenylhydantoin-induced

hyperplasia by antihistamines. Indeed, we have observed hyperplasia develop under the stimulus of diphenylhydantoin in two patients, not included above, who were taking chlorprophenpyridamine prior to administration of the diphenylhydantoin.

We were initially impressed by the possible relationship between histamine and the secondary changes, such as friability and erythema. Such a cause-and-effect relationship seems considerably less likely in view of our difficulty in obtaining an objective measure of the reversal of this phenomenon by antihistamines.

Summary

We have described an experience with the use of antihistamines in 31 patients with varying degrees of diphenylhydantoin-induced gingival hyperplasia, including 5 control patients who received a placebo in a double-blind experiment. We conclude that antihistamines do not reverse diphenylhydantoin-induced hyperplasia, though there is some indication that they temporarily relieve pain and, to a less extent, the edema, erythema, and bleeding in the more severely involved cases.

We wish to express our appreciation to Dr. Ernest Stark for interpretation of the pathologic material, and to Dr. Rupert Chittick for his help in making patients available at the Vermont State Hospital.

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The Electroencephalogram During Hypnotic Age Regression (to Infancy) in Epileptic Patients

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Introduction

This study of the electroencephalogram (EEG) in hypnotic age regression was suggested by a paper published by Kupper in 1945.[13] Briefly, Kupper found that in hypnotic age regression the EEG of an epileptic patient changed from an abnormal to a normal record when the patient was regressed to a period in his life antedating the development of epilepsy. This finding interested us, for it suggests that some changes occur in hypnotic age regession that are not directly elicited by suggestion, unlike other changes that result from direct suggestion. Furthermore, it seemed plausible that such changes in the EEG might be easily quantitated.

A brief review of the pertinent case reported by Kupper follows.

The patient was a 24-year-old merchant seaman with a history of grand mal seizures since the age of 18. Diagnostic studies were within normal limits with the exception of an abnormal EEG, which showed "diffuse cortical irregularities consistent with a convulsive disorder." The patient had no apparent neurotic traits other than immaturity and great dependency needs. Under hypnosis an emotional stress that precipitated the patient's first seizure was uncovered. In subsequent interviews hypnotic age regression was employed; and by this means the patient was regressed to his 12th birthday. An EEG recorded under these conditions was noted to be "within normal limits." "It remained so through succeeding suggested years until his eighteenth year in 1938, following the first attack. Then diffuse cortical abnormalities and slight spiking occurred. The record was then changed within normal limits by reassuring the patient and the series repeated. A convulsive seizure was produced and stopped while under hypnosis on suggestion of the examiner. Moreover, this could not be produced except by bringing up the specific triangular situation,"[13] involving the patient, his mother, and father.

Many reports have appeared in the literature in the interim dealing with changes in the EEG and in the neurologic and mental status of normal subjects during hypnotic age regression.[10,14,18,19] Likewise, pertinent aspects of the EEG in epileptic patients[3,4,5,7,11] have been studied. However, no investigation has dealt concomitantly with both aspects of this problem. While skirting this problem, Schwarz, Bickford, and Rasmussen[16] were unable to precipitate seizures or produce changes in the EEG's in 16 patients with convulsive disorders of probable organic origin having abnormal interseizure EEG's, using hypnotic suggestions to activate seizures. In 10 other patients with convulsive disorders, but with normal interseizure EEG's, these authors were able to precipitate seizures under hypnosis, but no changes were noted in the EEG's during the seizures.

Barker,[3,4] Dynes,[8] Ford,[9] and others[20] have shown that the EEG in hypnosis does

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not differ significantly from that recorded in the waking state, and that it is not a sleep variant. Likewise, hypnotic age regression of normal subjects produces no EEG changes.[14,19] Thus, one may not account for Kupper's findings on the basis that they represent variants produced by sleep or by regression per se.

That changes in affect are capable of producing alterations in EEG recordings of epileptic patients has been well established. Gottschalk [11] reported that the performance of silent mental arithmetic and the act of talking (regardless of content, if not of conflictual nature) either significantly reduced the frequency of abnormal high-amplitude, slow-wave paroxysms or had no noticeable effect on the frequency, but did not increase the incidence of these slow-wave bursts in any patient. Barker [5,6] was able not only to elicit abnormal EEG patterns in epileptic patients by recall of charged experiences but to induce convulsive episodes as well. Both these studies support one of the current concepts of the fit as a means for discharging the intense affect associated with an emotional conflict.[1,2,5,6,12,15,17]

In the present study, the primary object was to determine whether hypnotic age regression alone, without deep psychotherapy, produces alterations in the EEG of epileptic patients.

Method

The patients presented in this study were volunteers selected from the neurology clinic of the Cincinnati General Hospital outpatient department according to the following criteria: known "primary" convulsive disorders of grand mal type; abnormal interseizure EEG's, and a history of onset of seizures during adolescence. The patients were initially chosen at random and were later selected on the basis of responsiveness to hypnotic age regression, i. e., the ability to achieve sufficient trance depth for age regression. Anticonvulsant medications were not discontinued during these studies.

Two control subjects, a 25-year-old male medical student and a 19-year-old woman clerical worker, were also regressed to infantile levels and their EEG's recorded before and during the trances. Neither subject had a personal history of a convulsive disorder.

Waking EEG's were recorded just prior to hypnotic age regression with the patient or control subject in the supine position, using a standard 10-lead electrode placement on the scalp and ears. An eight-channel Grass Model III-D encephalograph was used for recording the EEG's. The supine position was maintained during hypnosis because it was comfortable during the lengthy procedure (up to three hours).

Trances were induced with relaxation suggestions, hand levitation suggestions, and/or ocular fixation methods, as described by Wolberg.[20] Increasing trance depth was achieved by suggesting limb catalepsy; involuntary movement; cutaneous sensibility changes; visual, olfactory, and auditory hallucinations, and, finally, fantasy. The patients were able to describe suggested fantasies and were later able to verbalize their "regression" experiences without awakening and with amnesia for the trance experiences on awakening. Regression was not attempted until the patients had achieved deep trance levels on several occasions as judged by posthypnotic amnesia. No attempt was made to record an EEG during the first regression attempt.

Regression was performed as suggested by Wolberg [20]; i. e., suggestions were made that the patient was getting younger, that his body was becoming appropriately smaller, and that he was once again the age suggested. In an attempt to differentiate "reliving" from role acting on the basis of current memory during hypnotic age regression, several methods were employed. The first method was described by True [18] and will be referred to as the True Age Regression Test. This method uses "*memorable* dates as chronologic landmarks" as the patient is regressed year by year. The patient is asked to name the day of the week corresponding to the event. Specifically, each of True's subjects was asked to name on what day of the week his birthday and Christmas fell in the particular year involved when regressed to these same days, and was scored on the basis of regression to ages 10, 7, and 4 years. Using this test, True found that approximately 80% of a group of 50 subjects gave entirely correct answers.[18]

The second method involves a test of the plantar response during hypnotic age regression. Gidro-Frank and Buch [10] reported three subjects in whom reversal of the plantar response to its infantile form (dorsiflexion) was observed in hypnotic regression. These authors state that the infantile response was obtained when the subjects were regressed to 5 to 6 months of age. In three other subjects who could be regressed to infancy, the dorsiflexion response was not obtained. Later

True and Stephenson[19] reported a group of six subjects, demonstrating the dorsiflexion response to plantar stimulation during regression to one month of age.

As a third check of the validity of the regression, each subject was asked to sign his name at various ages suggested in hypnosis.

Case Summaries

PATIENT A.—This patient was a 37-year-old white man who had had grand mal and petit mal seizures since the age of 14 years. His grand mal episodes occurred almost daily at first, chiefly at night. During these episodes, he was often incontinent of urine, bit his tongue, and suffered many falls. He was followed in the Cincinnati General Hospital psychiatric outpatient department from 1940 to 1952 and was transferred to the Neurology outpatient clinic with the diagnosis of idiopathic epilepsy and passive-dependent neurotic character disorder. In recent years he has had four types of attacks: (1) one to two grand mal seizures monthly, chiefly at night; (2) 60 to 80 petit mal lapses per month, (3) numerous "falls," which occur without warning, with complete consciousness, and (4) bizarre episodes of somatic "drawing" sensations. There was no family history of convulsive disorder. Projective studies in 1948 (age 27) indicated that he was of average intelligence with unsolved dependency difficulties, sexual maladjustment, and latent homosexuality. His past EEG's and the hypnosis record may be summarized as follows:

EEG Record.—Jan. 28, 1949: There were random slow and flat-topped waves of 4-6 cps and spike-dome complexes. Well-defined spike-dome activity occurred several times during attempts to calculate under pressure.

Oct. 15, 1952: Slow (5-7 cps) activity and, additionally, high-amplitude spike-wave activity after hyperventilation were present.

Sept. 16, 1954: The record was characterized by fast (14-18 cps) and slow (4-5 cps) activity, with high-amplitude bursts of 3 cps spike-dome activity, nonfocal.

Hypnosis Record.—The record obtained prior to hypnosis showed an admixture of fast (20 cps) and slow (5-8 cps) activity in all leads. Hyperventilation for two minutes produced no response. No paroxysmal activity was noted, and no focal signs were present. This record was essentially the same as one obtained 10 days previously, except that two paroxysms of 3 cps spike-and-wave activity were noted at that time. Hypnotic age regression produced no changes in the record. Impression: mixed fast and slow dysrhythmia without focal signs, and without change during hypnosis.

PATIENT B.—This patient was a 16-year-old Negro youth with no family history of convulsive disorder, who began having grand mal seizures at the age of 14 years. The seizures were usually nocturnal, characterized by "growling" sounds, thrashing of limbs, incontinence of urine and feces, tongue biting, and complete amnesia for the episodes. The boy had been an amateur boxer for several years, and had been knocked unconscious in a basketball game six months prior to his first attack. He had been free from seizures for a period of six months and was apparently in excellent health. The past EEG's and the hypnosis record are summarized.

EEG Record.—July 22, 1957: There was a 9-10 cps basic occipital pattern. The general tenor was one of irregular, slow (2-6 cps) activity in all leads. A bifrontal 3 cps pattern was seen in the left temporal area also, of higher amplitude and greater irregularity than that on the right. Impression: marked slow dysrhythmia with paroxysmal sequences and left temporal localization.

Hypnosis Record.—This record, taken in the summer of 1958, revealed an 8-10 cps basic occipital pattern, reflected at lower amplitude in the anterior leads. There were interposed throughout slow (4-6 cps) and some low-voltage fast (18 cps or more) activity. More of this slow and fast activity was encountered during hyperventilation than prior to hyperventilation. Hypnosis reduced movement artifact but did not essentially change the record. Impression: moderate, mixed fast and slow dysrhythmia; no focal signs or paroxysmal activity.

SUBJECT C (Control).—This subject was a 25-year-old white male medical student with no personal history of convulsive disorder. A paternal uncle had had grand mal seizures from early childhood, thought to be due to birth trauma.

Hypnosis Record.—The record obtained prior to hypnosis showed a 9-10 cps basic occipital frequency pattern, which was reflected at lower amplitude anteriorly. Hyperventilation for two minutes resulted in bifrontal slow (4-6 cps) activity of low amplitude. This persisted about 20 seconds after hyperventilation. No paroxysmal activity or focal signs were noted. The record was not altered during hypnotic age regression. Impression: activity within normal limits.

SUBJECT D (Control).—This 19-year-old white woman clerical worker had no personal or family history of convulsive disorder. She had had "temper tantrums" as a child and has had frequent mild generalized headaches in recent months, which she ascribed to worries in her job.

Hypnosis Record.—The record obtained prior to hypnosis showed low-amplitude 15-20 cps activity in all leads. Hyperventilation for two minutes resulted in short bursts of 3-4 cps activity, pre-

dominantly in the anterior leads. Occasional slow waves (3-5 cps) appeared for 50 seconds after hyperventilation. No focal signs were noted. The record during hypnotic age regression showed the same low-voltage fast activity as before. Impression: mild fast dysrhythmia, nonfocal in nature, with no change during hypnosis.

Results

As has been described above, no significant changes from the waking records were noted in the electroencephalograms of the patients and control subjects during hypnotic age regression.

There was no significant alteration in the plantar responses of patients or control subjects when regressed to ages of 1 year, 6 months, and 1 month.

Signatures obtained from the patients and control subjects at various "ages" during hypnotic regression appeared increasingly childlike as earlier ages were suggested. The signatures became progressively larger, and eventually all the subjects resorted to primitive separate block letters. The two patients used their childhood nicknames at the regression age of 7 years. Unfortunately, preserved specimens of childhood handwriting were not available for comparison with the samples obtained during regression in any case.

Results of the True Age Regression Test are presented in the accompanying Table.

Comment

Hypnotic age regression produced no significant change in the EEG's of the control subjects, confirming previous reports.[14,19] That this procedure produced no change in the abnormal EEG's of the patients does not confirm the work of Kupper. It does not refute his findings, since psychotherapy was not attempted in this study and no precipitating emotional factors were uncovered. Thus the question that arises concerning the influence of psychotherapy on the EEG during hypnotic age regression remains unanswered.

True Age Regression Test Results

Subject	Age, Yr.	No. of Chronologic Landmarks *	No. of Responses †	Correct Responses	
				No.	Per Cent
A	37	6	4	1	25
B	16	10	8	2	25
C (control)	25	8	2	1	50
D (control)	19	8	2	0	0

* Asked subject to give day of the week for Christmas and birthday at ages of 10, 7, and 4 years and at other ages.

† Subject felt sure of the day of the week (difference between the number of responses and the number of landmarks reflects the number of "I don't know" answers).

Kupper stated that "diffuse cortical irregularities" reverted to "normal" during regression, but did not further define the irregularities or the normalcy. Comparisons are difficult to make under such circumstances. There is no assurance that regression suggestions in the waking state without hypnosis might not have produced the effects observed by Kupper if the age suggested related to a nonconflictual period in the patient's life.

To assume that the epileptic patients reported here had "normal" EEG's during childhood is unwarranted, since no records were obtained during that period. This poses a problem for future studies also, because it is unlikely that a patient will have had an EEG recorded before the onset of his illness. Fortuitously, one of the control subjects in this study was found to have a fast dysrhythmia, as described, and the other control subject was found to have a family history of convulsive disorder.

Admittedly, the True Age Regression Test results suggest that neither patients nor controls were truly regressed. However, the applicability of this test as described is questionable if during hypnotic age regression the subject cannot name all the days of the week. Indeed, such was the case with one of the patients (B) in this study. When asked to name the days of the week at the suggested age of 5 years, he responded: "Saturday, Sunday, Tuesday, Wednesday, and Friday." When asked if there were any other days, he replied, "Holidays." Frequently answers of "I don't know" or "I can't tell" were encountered

in response to requests to name the day of the week. The assumption that birthdays and Christmas are significant, and are therefore "memorable chronological landmarks," to all subjects, is open to question.

Plantar stimulation during hypnotic age regression to infancy elicited equivocal dorsiflexion responses in both patients and one control subject (the clerical worker), but these responses were not sufficiently consistent to be considered significant. Thus far this altered response has been reported in only a small number of subjects, some of whom may have had enough medical training to prejudice the results. For example, one group consisted of student nurses.[19]

Whether the signatures were the product of true regression, or of conscious recall of past performance, cannot be determined, since authentic early samples for comparison were not available.

Summary

A brief review of the literature pertinent to hypnotic age regression is presented. Kupper observed that the "abnormal" EEG of an epileptic patient undergoing psychotherapy could be reverted to "normal" in hypnotic age regression to a time antedating the onset of seizures. His findings could not be confirmed by using hypnotic age regression alone.

Two patients with primary grand mal seizures were regressed in hypnosis to a time antedating the development of convulsions. No change from their waking records was observed in simultaneous EEG recordings during hypnotic age regression. Both patients had abnormal waking EEG's, as did one of the "control" subjects, who had no history of a convulsive disorder. The EEG's of the two "control" subjects also showed no change in hypnotic age regression.

The True Age Regression Test and the plantar response during regression to infancy, as measures of the validity of regression, were equivocal at best. Signatures obtained at various "ages" in hypnotic regression reflected increasingly childlike patterns.

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Minamata Disease

Late Effects of an Unusual Neurological Disorder Caused by Contaminated Fish

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Minamata is a small industrial town situated near the southwest coast of Kyushu, the most southerly of the three main islands of Japan. A number of villages are located on or near a neighboring bay. Into this bay flows the effluent from a large fertilizer factory. Between 1953 and 1956 a mysterious nervous disease affected the fishing community living near the bay. The outbreak was investigated by a number of departments of Kumamoto University, and the results were published in 1957, in Japanese in two supplements of the *Journal of the Kumamoto Medical Society*. The following brief account is taken from a recent article, summarizing the Japanese accounts of the outbreak (McAlpine and Araki [1]).

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Between November, 1953, and December, 1956, a total of 56 persons living on or near Minamata Bay were affected by a neurological illness characterized by an acute or a subacute onset of numbness and cerebellar signs. Deafness and disturbance of vision, increased salivation, and dysphagia were noted with varying frequency. The more seriously ill patients were confused, and many of these died (mortality rate 37%). The majority of those who survived were incapacitated in varying degrees. The main pathological finding was neuronal degeneration in the central nervous system, most marked in the granular layer of the cerebellum (Fig. 1) with reactive gliosis (Takeuchi et al.[2]). Experimentally, the disease could be readily produced in cats by feeding them with fish from Minamata Bay. The histological findings were similar to those found in human material, the granular layer of the

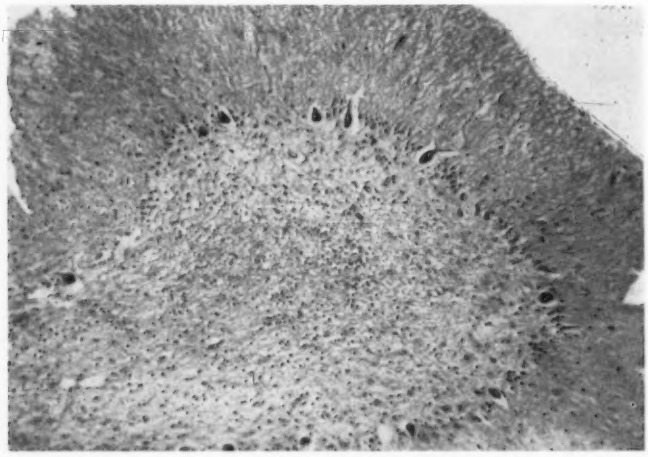

Fig. 1.—Neuronal degeneration in the granular layer of the cerebellum. Nissl stain.

cerebellum showing the most striking changes.

A detailed investigation by the Public Health Department of Kumamoto University (Kitamura et al.[3]) established the following epidemiological points: First, there existed a close relationship between the eating of fish and the occurrence of the disease. No breast-fed child was affected. Second, during the same period a fatal illness affected domestic animals, mainly cats, and scavenging crows which fed upon fish. Third, the fish responsible for the outbreak came from Minamata Bay, an observation later supported by the fact that following a ban on fishing in the Bay, which came into force in November, 1956, no further case had been reported, up till April, 1958. Lastly, chemical analysis of silt from the Bay suggested that the water was polluted. Two other observations of importance came to our notice in 1958—first, that some fish in Minamata Bay had died, and, second, that up till 1950 the effluent from the fertilizer factory had been diverted into the open sea; in 1950 the channel was closed, and a new one constructed which ran directly into Minamata Bay.[20]

Report of Cases

During two visits to Minamata, in February and March, 1958, we had an opportunity of observing the late effects of the disease in 16 patients whom we examined during a visit to their own homes. An additional six cases were seen in Kumamoto University Hospital. The following case reports are illustrative of the disease.

FAMILY E.—Visited on March 14, 1958.

The father, aged 48 in May, 1956, noticed numbness in both hands and a tired feeling in the legs. These mild symptoms did not progress, and he was able to continue at work. After some weeks he was symptom-free.

The mother, aged 43 at the beginning of May, 1956, developed numbness in the fingers of both hands, which, within a week, had spread to the feet and the lips. By the time she was admitted to a local hospital, on May 12, speech had become slurred, and she staggered in walking. During the next few months her condition slowly improved, and by 1958 the only residual symptom was slight numbness of the finger tips.

An 11-year-old son, in late April, 1956, developed indistinct speech and some difficulty in using chopsticks. No definite history of numbness could be obtained. His symptoms worsened, and by May 12, when he was admitted to hospital, he was unable to walk. At the time of his discharge, on Aug. 30, he had started to improve, and walking eventually became normal. A son aged 9 years had a history almost identical with that of his elder brother. His illness began in July, 1956, and reached its climax at the end of three weeks, by which time he was unable to walk without support. Progressive improvement followed a period of hospital treatment, and by the end of 1957 he was walking and speaking normally.

The youngest child, aged 5 years in May, 1956, was noticed to stagger when walking and often fell. Her speech became difficult to understand. When admitted to a local hospital, on May 12, feeding by nasal tube was necessary on account of dysphagia. She died two weeks later, following aspiration pneumonia.

A routine examination of fundi, reflexes, coordination, and pinprick sensation in the first four cases showed no abnormality.

The four oldest members of this family are married and live elsewhere. The fifth oldest sibling died some years ago. The parents and three of four of the remaining children were affected by Minamata disease in varying degree; all ate fish, and, to a less extent, raw fish.

FAMILY K.—Visited March 13, 1958.

The father, aged 23, was taken ill on June 17, 1954, with slurred speech, tremor of the hands, and unsteadiness in walking. He was admitted to Kumamoto University Hospital on July 18. No history of deafness or disturbance of vision was obtained. On examination the findings were dysarthria and marked ataxia in the limbs and on attempting to walk. Deep sensation was affected (no details given). The deep reflexes were present, and the plantar responses were flexor. On returning home at the end of August, his condition worsened, and he died in June, 1955.

A son, aged 5 years in April, 1954, caught cold and a week later was noticed to be weak on his left leg. Gradually speech became indistinct, and awkwardness in handling chopsticks and unsteadiness in walking were noticed. No history suggesting deafness, visual disturbance, or dysphagia could be obtained. After a few months, walking began to improve, although he continued to drag the left leg and the use of his hands was slow to return.

Examination revealed a shy boy with slight slurring of speech. Fundi normal; no nystagmus.

Hearing was apparently normal, but formal testing was impossible. Jaw jerk normal; no facial weakness. Power in all four limbs was diminished, especially in the left lower limb, which was mildly spastic. Deep reflexes were exaggerated, more so on the left, with an extensor plantar response. In walking he tended to drag the left leg. Minimal cerebellar ataxia was present in the limbs. No accurate sensory testing was possible.

A son, born Aug. 26, 1955, in April, 1956, when 8 months old, had an attack of measles, with a profuse rash and a temperature of 102-103 F for about a week. During this period and following it, he was entirely conscious, had no convulsions, and apparently made a normal recovery. However, three to four months later, his mother noticed that he could not sit up. Since then he has never talked or walked. He has been breast-fed up to the present time (age 2 years 7 months) and only recently has had any addition to this feeding.

The child cried continuously, and only a perfunctory examination was possible. There was no clinical evidence of hydrocephalus. His gaze appeared to follow a moving object, and he responded to a loud noise. All limbs were actively moved. Deep reflexes were brisker on the left than on the right. He crawled on a wide base but, nevertheless, frequently fell over.

There can be little doubt about the diagnosis of Minamata disease in the case of the father and older child. In the younger one, the absence of a history suggesting meningism, stupor, coma, or convulsions, and the interval of three months before any abnormality was noticed do not, on the whole, favor the previous diagnosis of measles encephalitis. On the other hand, the child was being breast fed at the time symptoms appeared, and the mother showed no evidence of Minamata disease, facts which make this diagnosis doubtful.

Case H. N.—A man, aged 43, in October, 1956, suffered from a large carbuncle on the back, which finally healed under treatment by his wife. In the middle of November he first noticed numbness in the fingers of both hands and a tingling sensation on the tongue. By the middle of December, both speech and hearing were affected, and at times vision became blurred. He began to stagger in walking and had difficulty in putting on his belt and in feeding himself, owing to numbness in the fingers. By the end of December, symptoms had reached their maximum severity, and from January, 1957, onward there was slow improvement, except for a short period in April, when numbness became intensified and was felt in the face for the first time. By March, 1958, speech had become nearly normal; he no longer staggered; hearing had improved, and only occasionally was vision blurred. However, slight numbness in the fingers and feet persisted.

On examination (March 14, 1958), the patient was cooperative. Fundi normal; no nystagmus; jaw jerk normal. No facial weakness or sensory loss. Speech slow and deliberate with occasional slurring. Hearing normal (rough testing). Power in all four limbs normal. Deep reflexes somewhat hyperactive but plantar responses flexor on both sides. Sensory testing showed some loss of superficial sensation, slight astereognosis, and faulty two-point discrimination in the fingers, but responses to passive movement were reasonably accurate. Vibration sense normal in lower limbs. Intention type of tremor present in upper limbs. Walking somewhat slow and deliberate; ataxia not in evidence.

This case exemplifies a good recovery from a typical attack of Minamata disease. The patient's wife and 19-year-old son were unaffected, although apparently they consumed about the same amount of fish as the patient. It is possible that an infection, i. e., carbuncle, precipitated the condition in the father.

Case K. S.—An unmarried woman. In the spring of 1954, at the age of 25, her parents noticed slurring of her speech, clumsiness when using chopsticks, and unsteadiness when she walked. These symptoms gradually progressed to the point that she was unable to stand, or even sit up. A temporary slight improvement in the early part of 1957 was lost after she had a generalized convulsion in September of that year. Since then she has been confined to bed, takes no interest, laughs without reason, and is doubly incontinent. No history of numbness, deafness, or visual disturbance could be obtained from her mother. Examination showed an emaciated and grossly demented woman, lying on a mattress; from time to time she had bouts of involuntary laughter. Owing to lack of cooperation, no detailed examination was possible. No gross loss of vision or hearing was detected; fundi not seen; no nystagmus; jaw jerk normal. Quadriplegia, with marked contractures at elbows and knees, was evident; plantar responses were bilaterally extensor.

Since the patient was unable to give a history, it is possible that numbness was present in the early stages of her illness. The clinical evidence of widespread cortical or subcortical and cerebellar damage was

similar to that found in severe and progressive cases of the disease.

The history of the next two cases was taken from notes published by the First Internal Medical Department of Kumamoto University (Katsuki, Tokuomi, et al.[4]).

CASE O.—A man, aged 41, a barber by trade, in the middle of October, 1956, noticed numbness in the fingers of the left hand, which four or five days later affected the right hand and both feet. By Oct. 25 it was present around the mouth and on the lips and had spread up to the elbows and thighs. Walking became unsteady, and, with increasing difficulty in using his limbs, he was forced to remain in bed. Between Nov. 8 and 10 speech became indistinct and hearing difficult, and he began to be troubled with insomnia. On Nov. 19, when he was admitted to Kumamoto University Hospital, numbness had spread to the lower part of the abdomen. The main findings were slurred speech; normal fundi and constriction of visual fields; pupils normal; no nystagmus. He was mentally alert. There was no paralysis, but a marked degree of ataxia was evident in the limbs and on attempting to walk. Superficial sensation was diminished in the limbs. All deep reflexes present; plantar responses flexor. During December deafness became more marked, and he complained of numbness all over the body and on the face. Ataxia was severer, and he could not stand without support. Both plantar responses were now extensor. By April, 1957, weakness of the limbs was noted, with early wasting of both hands. He became subject to myoclonic attacks. He was discharged in June, 1957.

When seen by us at his home on Feb. 20, 1958, he was in bed. According to his wife, further deterioration had occurred since he had left the hospital. She stated that he now takes little interest but is sometimes jealous of her. Whenever he is given any fluid or food, he has generalized "twitchings."

Examination revealed an apathetic, emaciated, deaf middle-aged man. Fundi normal; no nystagmus; bilateral weakness of lower facial muscles, and probably sensory loss around the mouth; remaining cranial nerves normal. Generalized wasting of limbs, especially marked in intrinsic muscles of hands, with mild degree of paresis. Upper limb reflexes depressed; knee jerks hyperactive but ankle jerks diminished; patellar clonus present but no ankle clonus; right plantar response equivocal, left of extensor type. Hypesthesia below both wrists and on feet, with postural loss in fingers and toes; no loss of pain sensation. Marked ataxia of all limbs on formal testing and patient unable to stand unsupported. Within a few seconds of drinking water he was seized with

Fig. 2 (Case O.; see text).—Photograph taken during a myoclonic epileptic attack.

generalized myoclonic movements, whose main effect was on the muscles of the trunk (Fig. 2). The patient remained conscious during the attack, which lasted about one and a half minutes.

A particularly severe case with slow progression and clinical evidence of widespread cerebral damage. The ataxia appeared to be both cerebellar and sensory in type. This was the only case in the series in which a myoclonic form of epilepsy was reported.

CASE KA.—A woman, aged 42, became ill on May 8, 1956, with numbness of the hands, which quickly spread to the forearms and around the mouth. During June, tremor of the arms was noted; speech became slurred, and within the next few weeks increasing unsteadiness finally prevented her from walking. Mental confusion, double incontinence, and involuntary movements of her limbs had developed prior to her admission to Kumamoto University Hospital, on Aug 30. At that time she appeared apathetic but occasionally burst into laughter or screamed. Choreoathetotic movements were constantly present, particularly in the upper limbs. No abnormality in fundi, motor power, reflexes, or sensation could be found. Mental confusion became worse, and at times she assumed an opisthotonic posture. Improvement dated from the administration of cortisone, and by Sept. 10 she was able to walk a few steps, though unsteadily. Improvement continued until May, 1957, when, during the course of 48 hours, she had a series of generalized convulsions, followed by a period of hypomania.

When seen by us at Kumamoto University Hospital on March 10, 1958, she presented a generalized coarse rhythmical tremor, which was more marked in the upper limbs than in the head or lower limbs, and which became accentuated on voluntary movement. At times an access of tremor led to violent shaking, which was usually accompanied by laughter and shouting. While walking, she would suddenly go backward but nevertheless managed to retain her balance, despite ataxia. No features of Parkinsonism were present. The remainder of the examination was essentially negative.

The character of the tremor suggested an interruption of striorubrocerebellar pathways. The patient cooperated well, was oriented, and we formed the impression that intellectual deterioration, if present, was probably mild in degree. (A hysterical overlay may or may not have accounted for the bouts of emotional overreaction and pseudoretropulsion.)

The following history of two sisters has previously been published by the pediatrics department of Kumamoto University (Nagano et al.[5]).

Case S. T.—A girl, in March, 1956, at the age of 5 years 11 months, had fever for one day. She was then observed to have difficulty in using chopsticks and in putting on her shoes. Within the next two or three weeks speech became slow and indistinct; she staggered in walking and often fell. On April 17 her mother noticed that the child appeared to have difficulty in seeing and in swallowing. She was unable to sleep and became agitated. On April 23 she was admitted to a local hospital, where two days later she had a generalized convulsion and nasal feeding became necessary. She was transferred to the pediatrics department on Aug. 30, by which time she had become drowsy and incontinent. Both hearing and vision appeared to be affected. Speech was dysarthric, and she was unable to stand unsupported. All deep reflexes were exaggerated, and the plantar responses were extensor. Subsequently there was no improvment.

When examined by us on Feb. 26, 1958, the child could not sit up, and was mute and apparently mentally defective, although deafness may have contributed to this impression. She appeared to see her mother and responded to a bright light. The pupils reacted, and the fundi were normal. Nystagmus was present on lateral fixation. All four limbs were flexed and spastic, with well-marked flexion withdrawal reflexes in the lower limbs.

Case J. T.—A younger sister of the preceding patient, on April 23, 1956, at the age of 2 years 11 months, developed indistinct speech and unsteadiness. By May 7, she was no longer able to walk; swallowing had become difficult, and she was incontinent. During the two months prior to admission there had been some improvement.

When examined by us, she was unable to sit up unaided and did not speak. She displayed pleasure when shown a tangerine, but made no attempt to grasp it. The disks were normal. She could move all four limbs freely. The deep reflexes were exaggerated and the plantar responses equivocal. Limb ataxia was not in evidence.

The disastrous effects of the disease on young children is illustrated by these two sisters. Mutism was confirmed by the mother in each child.

Comment

The complex and varied effects of Minamata disease are, in part at least, illustrated by the case reports. These clearly establish an initial phase of peripheral neuropathy. Numbness around the mouth, as experienced by some of these patients, has occasionally been reported in deficiency states (Denny-Brown[6]) and in association with neuropathy due to carcinoma (Henson, Russell, and Wilkinson[7]).

In the published accounts of Minamata disease, depression of the reflexes was noted only twice during the acute phase of the disease. With the exception of O., in whom we found depression of the upper limb reflexes and of the ankle jerks, the deep reflexes in those patients whom we examined were normal or exaggerated. Therefore it seems possible that the limb paresthesias were primarily due to involvement of the posterior root ganglia or the posterior columns. The information available to us, particularly with regard to postural and vibration senses in the early stage of the disease, was not sufficiently detailed to enable a conclusion to be drawn as to the likelihood of so-called "sensory neuropathy" (Denny-Brown[8]), although in a few cases a history of generalized numbness, associated with clumsiness of the fingers but without a history of motor weakness, was suggestive.

Cerebellar signs, such as slurred speech, ataxia, or tremor, were observed by us only in the more seriously affected patients. In the majority, although there was a clear history of such symptoms, residual signs of cerebellar deficit were either minimal or entirely absent.

Except in children, deafness was uncommon in the chronic stage of the disease. Impairment of vision was also noted by us in a proportion of the more severely affected patients. Perimetry in these cases was not possible, but during the original illness evidence of a generalized constriction of the visual fields was sometimes found; in no case was a central scotoma reported. In all patients whom we examined at a later stage the fundi were normal, with one exception. This concerned a boy who in 1954, at the age of 6 years, began to salivate excessively. Walking became unsteady, and vision deteriorated progressively, so that within two years he became blind. When examined, on March, 1958, he showed advanced optic atrophy unassociated with chororetinitis, mild right-sided weakness, bilateral extensor plantar responses and cerebellar ataxia in both upper limbs. The Wassermann test had not been carried out, but the picture did not suggest congenital neurosyphilis. The year of onset, the initial sialorrhea, and the clinical findings, apart from the optic atrophy, favored a diagnosis of Minamata disease rather than a demyelinating disease.

Dysphagia was mentioned in several hospital case reports as an occasional early symptom, but we did not encounter it or other clear-cut brain-stem signs as late sequelae, with one exception—Case Ka., in in which a red-nucleus type of tremor may have been due to a midbrain lesion.

So far, the effects of the disease on the peripheral nervous system, cerebellum, and special senses have been considered. In addition, a number of cases showed widespread cerebral changes. The published accounts of the acute phase of the disease emphasize the prominence of insomnia, mental confusion, stupor or coma (in the fatal cases), convulsions, and involuntary movements, thus providing clear evidence of diffuse encephalopathy. In some of the patients whom we examined more than two years later, evidence of intellectual deterioration was present; and in a few instances this appeared to be progressive, a finding which, along with epilepsy of late onset and increasing limb spasticity with incontinence, suggested a progressive form of neuronal degeneration. Case K. S. falls into this group. Although involuntary movements were reported in several patients during their acute illness, we did not observe Parkinsonism or chorioathetosis as a sequel.

The severe effects on young children are apparent from the description of the disease in the T. sisters. Mutism was noted in five children whom we examined, aged from 4 to 8 years. In three of these children this defect was doubtless due, in part, to deafness. In four of the six children originally admitted to the pediatrics department during the acute phase of the disease vision was stated to be affected. One of the T. sisters and one other child seen by us had defective vision with normal fundi, suggesting a cortical type of blindness, particularly as the presence of gross mental impairment and quadriplegia provided other evidence of widespread cerebral damage.

With a disease so widespread in its effects on the nervous system, evidence of myelopathy might have been expected. However, with the exception of Case O., in which there was wasting, particularly of the intrinsic muscles of the hands, such evidence was lacking in those patients whom we examined in the chronic stage of the

Fig. 3.—Child aged 4 years 6 months—mute and severely quadriplegic.

disease. When pyramidal signs were found, widespread cerebral damage appeared to be the explanation.

On the whole, there was a fair amount of agreement between the clinical and the pathological findings. Owing to the fact that attention was fixed on the cerebral manifestations of the disease, histological confirmation of neuropathy was lacking. The marked and constant fall-out of cells in the granular layer of the cerebellum adequately explains the cerebellar signs; likewise, the widespread neuronal degeneration in the cortex is consistent with the clinical picture of encephalopathy, while the presence of gliosis would account for the progressive deterioration in some of the more seriously affected patients who survived. Viewed broadly, the histological findings were not those of encephalitis but were consistent with a widespread toxic process with a special predilection for neurons.

Etiology

It is not our purpose to discuss this question in any detail, but some reference must be made to it in the light of the clinical findings. As previously stated, the cause of the outbreak has not yet been determined; but on theoretical grounds the action of either a thiaminase or a toxic agent must be considered.

Thiaminase.—The association of neuropathy with deafness and impaired vision suggested to us that the clinical picture of Minamata disease might be explained in terms of a deficiency disease due to the action of a thiaminase contained in raw fish. In 1941 Green and his associates [9] described a neurological disorder (Chastek paralysis) which had developed in foxes fed on a diet of raw carp. Jubb and his colleagues [10] have recently reported their findings in cats brought to them because of an illness caused by a diet of canned commercial cat food containing whole fish. Anorexia was followed by ataxia, suggesting cerebellar dysfunction. Convulsions were a transient feature during the critical phase of the disease. A quick improvement usually followed the injection of B group of vitamins. Prominent among the histological findings in the severely affected cats were focal and bilaterally symmetrical hemorrhages in the periventricular gray matter; these were seen less constantly in the vestibular, oculomotor, and red nuclei, and in the mammillary bodies. The authors refer to previous work in cats, in which an acute neurological disorder was caused by a diet containing dog food and brewer's yeast autoclaved to destroy thiamine (Everett [11]), or by a diet of carp or salt-water herring (Smith and Proutt [12]) both of which were shown by Deutsch and Hasler [13] to contain a thiaminase. In these experiments a rapid response followed injections of thiamine. Jubb and his associates consider that the naturally occurring disease which they encountered in cats is analogous to that observed experimentally by Everett and Smith and Proutt. They conclude that it is due to thiamine deficiency resulting from the inactivation of the vitamin by thiaminase present in fish.

Turning to the human form of Minamata disease, signs such as ocular pareses and nystagmus, both conspicuous features of the cerebral picture produced by thiamine deficiency, were not observed, nor were the characteristic hemorrhagic lesions in the mammillary bodies or upper brain stem reported in a single fatal case. Likewise, in the cat form of the disease hemorrhages were not a feature. Furthermore, neuronal degeneration in the granular layer of the cerebellum, a striking feature of Minamata disease in both human and cat material, has not been reported in any of the nutritional disorders of the nervous system.

Additional reasons for believing that Minamata disease is not due to the effect of a thiaminase are as follows: 1. The eating of raw fish, more particularly by fishermen and their families, is customary throughout Japan; yet, as far as we could ascertain, no similar outbreak has previously been reported. 2. According to Fujita,[14]

thiaminase is found mainly in certain varieties of fresh-water fish in Japan, and, with the exception of shellfish, the salt-water fish which he tested contained little or none of the enzyme. In the majority of the affected families the amount of shellfish consumed was small as compared with other varieties of sea fish. 3. Cooked, as well as raw, fish appeared to cause the disease. Thiaminase is destroyed by cooking. 4. The fish in the Bay were themselves affected, suggesting the action of an extrinsic poison.

A Toxic Agent.—In our previous paper we referred to the results of chemical analyses of human and animal material, of fish, and of the silt from Minamata Bay, carried out independently by a number of departments of Kumamoto University. We stated that there was general agreement that a toxic factor in fish had been the cause of the outbreak, but its chemical nature had not been determined.

The effect of certain metals on the nervous system may resemble to some extent those met within Minamata disease. The best known are the compounds of methyl mercury, which may cause ataxia, dysarthria, constriction of the visual fields, occasionally an extensor plantar response and, experimentally, peripheral neuritis (Hunter, Bomford, and Russell [15]). Thallium intoxication may produce a complex neurological picture—psychosis, choreiform movements, inversion of sleep rhythm, deafness, retrobulbar neuritis with optic atrophy, ocular paresis, bulbar palsy, pyramidal signs, and polyneuritis. In severe cases convulsions may be followed by coma and death (Prick, Smitt, and Müller [16]). Cerebellar signs have not apparently been described. We have been unable to find any reference to neurological symptoms resulting from chronic selenium intoxication, although mild psychiatric symptoms have been described (Lemley and Merryman [17]).

Degeneration in the granular layer of the cerebellum, which is a conspicuous feature of Minamata disease, is nonspecific; it may occur in a variety of conditions, such as hypoglycemia, hyperglycemia, mercury intoxication (bichloride and methyl compounds), and chronic alcoholism (Leigh and Meyer [18]; and Neubuerger [19]).

Manganese, selenium, and thallium have received most attention from those investigating Minamata disease; only thallium would seem capable of producing the main clinical features of this condition.

Dr. Leonard T. Kurland, National Institutes of Health, Bethesda, Md., and Dr. Bruce Halstead, of the Tropics Research Institute, Loma Linda, Calif., were invited by the Japanese authorities to collect specimens for chemical and pharmacologic analysis. The results of these analyses of fish, shellfish, sea water, and silt from the Bay may throw further light on the identity of the toxic substance.

Whatever may be the nature of the chemical compound responsible for this disorder, its probable action is on enzyme systems, as originally suggested by Katsuki and Tokuomi.

Summary

Between 1953 and 1956 an unusual neurological disorder affected inhabitants of fishing villages near Minamata Bay, Kyushu, Japan. The epidemiological, clinical, and other aspects of the outbreak, as originally published in Japanese by the staff of Kumamoto University, are briefly summarized.

Characteristically, Minamata disease affects the peripheral nervous system, the cerebellum, hearing, and vision. In severe cases encephalopathy may be followed by signs suggesting progressive brain damage.

The main histological finding is widespread neuronal degeneration, particularly in the granular layer of the cerebellum and in the cortex.

The sequelae of the disease, as observed in 22 cases, are described.

Etiology is briefly discussed, with special reference to a deficiency factor or a toxic agent.

Circumstantial evidence suggests that Minamata disease is due to the toxic action of a chemical compound contained in the effluent which flows into Minamata Bay from a nearby fertilizer factory.

In acquainting ourselves with the background of Minamata disease, we were greatly helped by those who had undertaken the original investigations; we wish also to thank Prof. Y. Kawamori, Assist. Prof. H. Tokuomi, and Prof. S. Nagano for the opportunity of examining patients under their care. Prof. T. Takeuchi generously gave us pathological sections, from which Figure 1 was taken. Our visits to Minamata were made possible through the kindly cooperation of Prof. R. Miyagawa. We are also grateful to Dr. J. R. M. Innes for drawing our attention to the work of Jubb and his colleagues.

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Editorial

Compensatory Mechanisms in Occlusive Vascular Disease of the Brain

The Anatomical Basis

It seems reasonable to assume that after occlusion of one of the major blood vessels of the brain adequate compensatory or collateral circulation must develop in order to confine the resulting brain softening within minimal limits, as well as to provide adequate channels for recovery of the brain tissue. As in the case of other forms of cerebral vascular disease, there are many unresolved issues which confront the clinician after thrombosis or embolism of a brain vessel. Chief among these is the problem of the anatomical basis by which compensatory circulation is provided, once a vessel has been closed by thrombosis, embolism, or atheromatous degeneration.

Anatomy of the Circle of Willis

Though anatomical studies of the configuration of the circle of Willis are available, clinical neurology appears to have had difficulty in making fruitful use of them. It has been known for some time that anomalies of the circle are common, but for the most part this fact has been tucked away as an interesting anatomical observation without clinical importance. It is difficult to escape the conclusion that anomalies play a significant role in the compensatory circulation following vascular occlusion and that, apart from the factor of disease of the vessels, collateral circulation within the circle itself should be more efficient in a normal than in an abnormal circle of Willis. All available investigations indicate that in only about 50% of cases is there a true, normal circle. In a recent study of 350 dissections of the circle of Willis in normal brains, a normal circle was found in only 52.3% (Alpers, Berry, and Paddison [1]).

The vertebral-carotid relationship is maintained for the most part in the circle of Willis. A complete separation of the two segments of the cerebral circulation due to absence of both posterior communicating arteries has been reported only rarely. In similar fashion, the connection between the two sides of the cerebral circulation through the anterior communicating artery is rarely lost. It seems quite apparent, therefore, that insofar as the side-to-side and anterior-posterior connections of the circle of Willis are concerned, there is a large factor of safety.

On the other hand, anomalies are frequently present which may have clinical meaning. More of these involve the posterior part of the circle, particularly the posterior communicating arteries, where string-like vessels with narrowed lumens are common (26%) on one or both sides. Despite the narrowed channels seen in the anomalous string-like vessels, there is no decisive evidence that the vertebral-carotid circulation is embarrassed under normal circumstances. Or, it is safe

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to say that there appear to be no recognizable clinical symptoms which result from narrowed posterior communicating channels. If, on the other hand, occlusion develops in either the internal carotid or the vertebral circulation, a string-like posterior communicating artery may interfere with compensatory circulation from either of the segments of the circle of Willis, particularly if the posterior communicating artery is further narrowed by atheromatous changes. Evidence appears to be accumulating which indicates that with the development of atheromatous disease and changes in pressure relationships between the vertebral and the carotid segment of the circle of Willis, each of these becomes quite dependent on blood supply from the other. What develops in the brain after internal carotid artery occlusion may be greatly affected by the condition of the vertebral-basilar segment, and both segments, in turn, are dependent on the condition of the posterior communicating artery. This holds true for the development of compensatory circulation within the circle of Willis itself.

Under some circumstances the posterior communicating artery may be absent on one side, the artery of the other side remaining normal or being string-like. It is easy to visualize in a condition such as this the importance of establishing compensatory circulation through the other side, where the posterior communicating artery is still present, or by means of extracranial channels on the side of the absent artery, in the case of occlusion either in the carotid or in the vertebral segment of the circle of Willis. That such compensation may become established if there are good side-to-side connections by means of the anterior communicating artery is easy to imagine, but this may be impaired or lost in the presence of disease of this artery. On the whole, there is a large factor of safety by means of duplicate and triplicate anterior communicating arteries, but this vessel is as often single as it is multiple, and narrowing or occlusion of its lumen may seriously interfere with side-to-side compensation, which is vital in the presence of an absent posterior communicating artery of one side.

What role is played by multiple anomalies of the circle of Willis is difficult to evaluate. These are very common and involve many patterns. One of the commonest, to cite a single example, consists of a string-like posterior communicating artery, or one preserving the embryonic derivation of the posterior cerebral from the internal carotid artery, and duplicated anterior cerebral vessels. It is only possible to reflect that multiple anomalies must play fully as significant a role in compensatory brain circulation as do single ones.

One of the common anomalies of the circle of Willis is that of emergence of the posterior cerebral from the internal carotid artery (15%), readily seen by arteriography. With development of occlusion of the internal carotid artery in the neck or within the skull below the junction of the two vessels, it can readily be seen that an embryonic posterior cerebral artery could serve as an important means of supplying compensatory circulation from the vertebral-basilar segment of the circle of Willis. In middle cerebral artery occlusion it has been possible by arteriography to observe dilatation of an embryonic posterior cerebral artery, as a means of collateral circulation.

The conclusion seems inescapable that anatomical variations in the circle of Willis are important in occlusive vascular disease for the establishment of compensatory blood flow through the circle itself. Unfortunately, there is no means of predicting or demonstrating in life the configuration of the circle.

The problem naturally arises whether there is a relationship between the incidence of brain softenings and anomalies of the circle of Willis. In a study of 194 brains with softenings (Berry and Alpers [2]) a normal circle was found in only one-third of the specimens, as compared with 52% in normal brains. In this same series, absence of vessels was found in 1.5% (normal 0.6%); string-like vessels were observed in 43% (normal, 26%), and duplicated vessels, in 19% (normal, 17%). In hemorrhage no change from normal was found. Brain softening due to vascular occlusion appears to be more frequent in the presence of anomalies of the circle of Willis, especially of string-like posterior communicating arteries.

Compensatory Mechanisms in Vascular Occlusion

Indirect evidence of the role of compensatory circulation is readily seen after occlusion of one of the major blood vessels of the brain. The brain may react to such an occlusion by no softening, minimal softening, or breakdown of tissue of varying extent. Pathological studies reveal that this is true in the case of internal-carotid and basilar-artery occlusions. When frank softening develops after occlusion of the internal carotid artery, it maximal extent is found in the middle cerebral artery distribution, the anterior cerebral escaping in most instances (Berry and Alpers [3]). In other instances of internal carotid artery occlusion, when enough time has elapsed for complete breakdown of tissue, there may be no softening whatever, incomplete softening, or small areas of breakdown of tissue of varying extent. The basis for these variations, in the case of occlusion of any vessel, is in part anatomical, and is dependent on the efficacy and extent of the compensatory circulation.

The available compensatory channels after vascular occlusion have been studied largely by means of arteriography. Though this method has shortcomings, it at least provides information, necessarily incomplete, regarding collaterals in the living subject. In the case of internal carotid artery occlusions compensatory blood flow is established by the following channels:

1. Through the circle of Willis, from the opposite internal carotid artery
2. Through the external carotid artery of the side of occlusion by its various branches into the ophthalmic artery
3. From the vertebral system through the circle of Willis
4. Through the external carotid artery into the vertebral system
5. Through the ipsilateral anterior and middle cerebral arteries

The channels of collateral blood flow for other vessels remain to be determined, and it is probable that other channels exist for carotid occlusions. It is quite probable that a study of a large series of occlusions would demonstrate that there are patterns of compensation, but that the development of compensatory circulation is an individual one, dependent on many systemic factors. The role of meningeal anastomoses in the development and containment of softenings is not yet clear (vander Eecken, Fisher, and Adams [4]). It remains to be determined whether blood may be sent in significant degree through meningeal anastomoses, from one area of supply to another.

The Problem of Thrombosis

The opinion has gained ground that thrombosis as a cause of brain softening is rare or uncommon, and that it cannot usually be found at autopsy. From this has developed the concept of infarction without evidence of occlusion, and the

belief that necrosis or softening of brain tissue may result if vascular insufficiency is maintained for a sufficiently long period. In a study of 354 pathological specimens with softening, thrombosis involving one of the larger cerebral vessels was found in 75%, where the clinical diagnosis indicated its probable presence and the vascular tree was carefully investigated for such occlusion (Berry and Alpers [2]). It is clear from this study that thrombosis is not rare and that, when sought for in proper cases, it is usually found. The crucial group is composed of the 25% in which no thrombosis is found. It remains to be determined whether thromboses can be found in such instances. In the case of softenings involving small, deep-penetrating vessels, failure to demonstrate thrombosis cannot be regarded as conclusive without serial-section study of the affected areas. From an anatomical standpoint it is difficult to see how actual breakdown of tissue, resulting in frank softening, can develop without occlusion of a blood vessel.

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The Neurology of Motivation

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The Nature of Motivation

"Behavior," as defined in Webster's, is the "mode of conducting oneself," and, as the word "oneself" denotes, includes activities of the total organism in relation to its environment. Now these activities, to constitute behavior, must be characteristically purposeful, goal-directed, or "motivated." To walk is not to behave, but to walk to a political meeting and to take a position on the issues is to behave. The purpose or goal determines the quality of the behavior. To shoot a gun, again, is not to behave, but to shoot a gun in war and to shoot it in murder, although quite the same in motor mechanism, are nevertheless vastly different kinds of behavior. I think we may agree that any biological science of behavior must therefore consider goals or motivation as the unique hallmark of behavior.

For centuries the philosophy of science has been deterministic and has had no place for motivation. The achievements of science, particularly of human medicine, have resulted almost exclusively from our adherence to determinism. We reason today from cause to effect, and it is not our habit any longer to consider "purpose" as a cause. Yet we recall that Aristotle, the first scientist, and one of the greatest, included "purpose" as an effective cause. For him it was the "nature" of an object, whether living or not, to develop toward an end which was immanent from the first and determined the object's changes.[1] This teleology—the thought that events happen in order to reach a goal implicit from the first—we eschew today in scientific discussion, but resort to incorrigibly in daily thought and speech—e.g., the kidney operates in order to excrete urine; leukocytosis occurs to combat infection; the sunflower turns to the sun to receive more light. Even in the hospital ward and clinic, it is often said that the neurotic is *motivated* by hope of some gain. This teleological habit of thought is the central core of theology, which begins with God's purpose, and which is still powerful in society today. Modern dynamic psychology, in its attempt to found a "science" of behavior on purpose, returns to the teleology of Aristotle, and actually reifies or objectivizes our *sense* of free will, which it elaborates into id, ego, and superego, as the effective causative force in behavior. This sense of free will is the most inescapable and immediate quality of subjective experience, no matter how solemnly we may, on scientific principles, rationalize it out of existence.

The biological psychiatrist especially is a split personality. On the one hand, his deterministic concept of behavior as the resultant of genetic and environmental factors operating through the nervous system distinguishes him from the "dynamic" psychiatrist. He refuses to consider modern indeterminacy, as conceived by Eddington and the atomic physicists,[2] as a breach in the wall of rigid determinism. But as a citizen in his private doings, he consults his own desires, seeks his own goals, and exercises his own choices with a full and conscious sense of "free will." He never allows his theoretical determinism to interfere with his personal freedom in his choice of a cigarette or of a wife. This division of his mind into two watertight compart-

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ments is as obvious as that of a hysterical patient, and the apparent mutual inconsistency of his two attitudes scarcely strikes him as needing resolution.

Let us not underestimate the sense of free will. Human beings refuse to give it up: It is too immanently present in every one of us, who feels that he can sit down or stand up, as he chooses. It is fundamental to each man's sense of personal responsibility (how be responsible without autonomy?), of aspiration (how strive for excellence without unfettered choice of one's acts?), of personal dignity (how preserve one's self-esteem without the pride of chosen principles of life?). Without doubt, freedom of choice is the most precious and subjectively indispensable ingredient of human individuality. Must we, to be consistent, abandon these prerogatives in favor of our cherished scientific determinism? This dilemma is the central problem of the dynamics of human behavior. If the nervous system is, as it seems to be, the organ of behavior, and the most characteristic element in behavior is its motivation, what then of the neurology of motivation?

It remained for Charles Darwin to devise the concept of the surival of the fit—a concept extending to "traits" beneficial in the struggle with the environment, thus avoiding the appeal to "purpose." For example, the flamingo has long legs and neck not "in order" to get food from shallow lakes but "because" these features, occurring, as it were, accidentally, aided him in surviving. Thus, the cause precedes, and does not follow, its effect. So we think that leukocytosis occurs because it is induced by infection through chemical or enzymatic action, a process which exists because organisms without it have perished. We cannot doubt that human behavior, with its overtones of subjective motivation, has likewise promoted the survival of the race and obeys the same biological laws. It seems wise, therefore, to see whether human motivation can be understood in familiar deterministic or neurologic terms. If the nervous system, together with its chemical and humoral adjuvants, is the organ of behavior, it must be the organ of motivation.

Now a characteristic quality of behavior is that it is dynamized (or driven) by *affect*, which is the organism's subjective evaluation of, and attitude toward, a situation. Subjectively, affect is a broad spectrum of attitude, from the subtle nuances of preference to the extremities of passion. Whatever I *feel* about things experienced is my affect. When Adam or I see an apple, it is our affective attitude which "*induces*" us to eat it or not. Likewise, whatever I feel about things *imagined* is my affect. When I imagine your approval of this paper, it is my affective attitude which induces me to write it. (Of course, I might have imagined your disapproval, and so been induced not to write it. I take a chance here!) Thus, my motivation in eating the apple, or in writing this paper, or in doing anything else, is affective. Unfortunately, there is no neurophysiological term corresponding exactly to subjective affect. The role of affect in behavior certainly includes both the visceral response and the activation and direction of the extrinsic motor response. The term *behavioral drive*, including both visceral and extrinsic elements, might be used for the neurophysiological processes corresponding to subjective affect, but we shall need to remember that, like affect, behavioral drive may be positive or negative. Motivation, then, is affect, and affect is behavioral drive, positive or negative.

Biologically considered, the beginnings of animal behavior appear to be driven by certain primal needs—food, safety, and sex. There is no difficulty in understanding how these needs activate appropriate drives, established by natural selection and expressed through preformed or inherited neural patterns of reaction. As the organism gains experience in its contacts with the environment, the original drives remain unchanged but come to be evoked by more derivative needs and expressed through more and more complicated patterns with

the process of conditioning.* The organism *learns* to accept originally neutral stimuli as now significant in the search for food, safety, and sex. So the drives express themselves by means of ever more complex behavior, culminating in adult habits which, in the aggregate, constitute character. One may then picture the cat as "driven" by need to roam by night "in search of" its simple satisfactions, or the eager scientist as "driven" to toil by night by his need for more complex rewards.

From the psychological viewpoint, such biological drives must be experienced as the *affective desire* for the satisfaction of the same primal needs: food, safety, and sex. Simple at first, such motivations become more complex with experience, and express themselves in more and more indirect and tangential efforts toward gratification. They may be directed, for example, toward achievement or aggrandizement, and take their paths through numerous preparatory and anticipatory goals, such as the invention of tools, the passing of examinations, the learning of a science, or the practice of medicine. It is my suggestion, then, *that affective desire or motivation is the subjective experience of a behavioral drive by an original or acquired biological need, which constitutes a stimulus to "goal-seeking" behavior.* This may easily be seen in such simple formulae as those in Figure 1.

What an observer sees in another as a deterministic behavioral drive stimulated by need is experienced in himself as a motivation toward the satisfaction of the same need. The processes of life are thus a stream of events which, viewed from within, constitute subjective experience, with all its qualities of desire and freedom, but, seen from without, are a deterministic sequence. Motivating desire thus becomes the subjective experience of the deterministic biological reaction, just as vision is the subjective experience of neuro-optical processes. In this fashion, Aristotelian teleology becomes only the subjective aspect of a deterministic sequence as we understand the term.

Certain normal variations in the physiological state alter the *need* which we have hypothesized as the source of "motivation," both quantitatively and qualitatively. For example, the normal hyperactivity of childhood creates a need for large amounts of carbohydrate, a need leading to hunger and the "motivation" for eating sweets and

* It has been our conception that this process of conditioning, so important in the neurology of behavior, as in the psychology of learning, takes place in the cerebral cortex. However, most interesting recent electrographic physiological work by Hernándes-Peón et al.[a] demonstrates that conditioning to sounds may take place even in the cochlear nucleus itself. Similarly, Yoshii, Pruvot, and Gastaut [b] have shown that conditioning may occur also in the ascending reticular activating system. It begins to appear that the process of conditioning is possible at many levels of the nervous system, and that it is a property of the synapse and may occur as a process of sensitization of neuronal networks to coded signals.

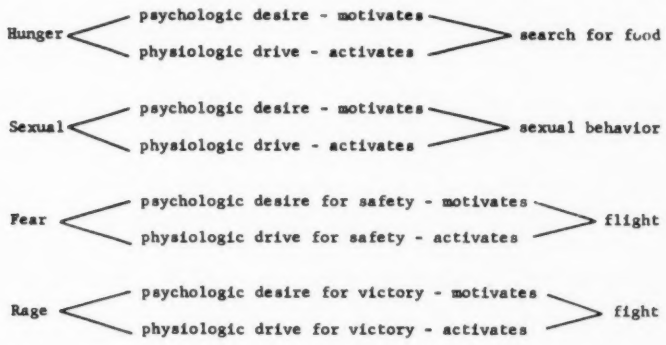

Fig. 1.—Physiology of motivation. Psychological motivation and physiological drive are but different aspects of the single process of satisfying a biological need.

other food. Again, normal fatigue produces the need for rest and sleep; hence it "motivates" the search for these restoratives.

Inevitably, conflicts arise which oppose one activation or drive against the other, thus offering the organism a "choice" of two courses. Physiological conflict between the need for rest and the drive to play may result in the familiar sight of the child striving bravely to remain awake, with drooping eyelids. Hunger may activate to a search for food, while danger activates to flight. Or a single situation of danger may activate alternatively to flight or fight. In such conflicts, the issue may be decided by the relative degrees of conflicting needs (there may be more need for food than for safety), or by the material circumstances of the environment (the food may be unattractive and the danger great), or by the person's habitual character structure (he may fight or flee, as his experience has taught him). The final action is the algebraic sum of conflicting drives. In so-called complex personalities the conflicting needs and drives may be so numerous and variable as to make the resultant difficult to follow or predict. Biological determinism needs no "free will" to explain such decisions; yet the subject experiences, at the moment of decision, a *sense* of free will. As biologists, we cannot ignore the objective variables which determine the decision, but we may not deny to the subject his keen sense of autonomy in making his decision. We can only observe that the sense of free will is correlated with and occurs simultaneously with the deterministic resolution of conflict. As motivation is the affect experienced when need drives to action, so free will is the more precise affect accompanying behavioral resolution of conflicting drives. It is as though the answer to the battle cry of free will, "I can do what I please!" may best be answered, "You can do nothing *except* what you please!" If we conclude that free will is but an illusion, we must nonetheless admit that it is an unfailing and immediate experience, of priceless value to us as men; indeed, a precious illusion (Masserman[5]).

Well-known pathological conditions in medicine and neurology likewise influence "motivation." The physiological need for sugar in the patient with diabetes mellitus "motivates" his desire for carbohydrates, while the similar need for water which will maintain isotonicity determines his "motivation" for drinking. The patient with thyrotoxicosis needs a cool environment and much food; the patient with cardiac decompensation needs air and rest, and these needs "motivate" his behavior. One might continue with such illustrations at great length. Finally, the "need" may be much more complex than that for food or drink. The person with physical defects or conditioned psychological feelings of inadequacy needs the satisfaction of physical or mental achievement and so is driven or motivated to great effort, as a Byron swimming the Hellespont, or a Napoleon or a Hitler drenching the world in blood.

We have seen that primitive or instinctive needs (desires) constitute unconditioned stimuli, while secondarily acquired needs are engrafted upon these as conditioned stimuli. Thus, mature behavior is determined in the adult nervous system by means of a complex system of neuronal and hormonal linkages resulting in the subjectively "motivated" acts of the individual. Dell has admirably sketched these mechanisms by which the organism reacts, both internally and externally, to its many "needs."[6] Thus, behavior becomes the product of innumerable needs as stimuli, often in conflict or in cooperation with each other. Under the impact of environmental stimuli, these needs set the "goals" for the personality, and their organized drives constitute the character of the individual.

Mechanisms of Motivation

To understand the neurology of motivation, we shall need to study the ways in which inborn and acquired needs "drive" human behavior. Since we have seen that motivation is affective, we are concerned,

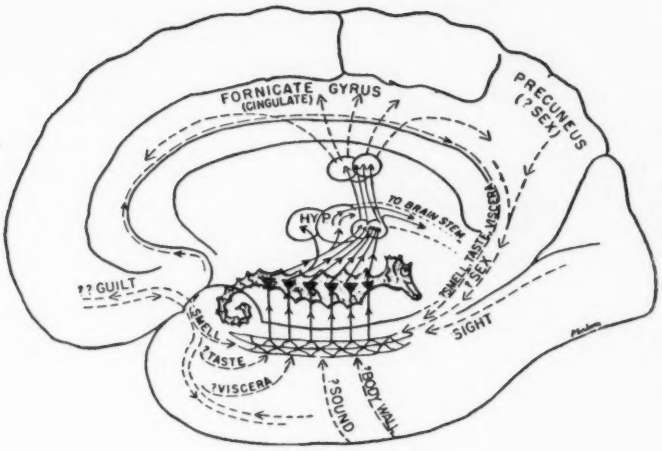

Fig. 2.—Visceral brain. Explanation in text. Afferent impulses of all modalities reach the hippocampus, where affect (behavioral drive) is added. *HYP* is hypothalamus, directly behind which are mammillary bodies, the anterior thalamic nuclei lying just above. Reproduced from article by Paul D. MacLean entitled "Psychosomatic Disease and the 'Visceral Brain,'" published in *Psychosomatic Medicine* (11:338, 1949), by permission of the publisher, Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers).

therefore, with the neurology of affect, about which our knowledge is rapidly enlarging. "The Papez circuit," named for the late neuroanatomist whose hypothesis, proposed in 1937,[7] has been so signally confirmed by subsequent work, was the beginning of our understanding of the importance of the visceral brain in affect (Fig. 2).

Electrography in the intact animal has shown that neural impulses arising from sensory stimulation through all modalities find their way to the hippocampus.[8] Thence they pass through the fornix to the mammillary bodies, and then on by way of the mammillothalamic bundle to the thalamus, and, finally, to the cingulate gyrus and, presumably by transcortical pathways, to other cortical areas and back to the thalamus. From the mammillary bodies and probably also from the thalamus itself, as well as from the ascending reticular activating system, the hypothalamus is stimulated, and so, as the head ganglion of the autonomic nervous system, leads to the visceral accompaniments of behavior. These exceedingly simple circuits are no doubt supplemented and elaborated by other pathways. The important fact is that much clinical, pharmacologic, and experimental evidence (to be discussed in part below) indicates that this so-called visceral brain is the chief central arena for the neurology of affect, or, as we have called it, behavioral drive. It must be, then, the scene where the processes of motivation have their physiological correlates.

Much experimental work demonstrates how important in affect, and therefore in behavior, the various anatomical structures in the visceral brain are. One cannot even summarize this work here; such summaries are available in the literature.[8] But one may mention the classical observations of Klüver and Bucy[9] on monkeys subjected to bilateral temporal lobectomy which removed the amygdala and much of the hippocampus, thus breaking the Papez circuit in its most important segments. Affect was almost abolished in such animals, to the extend that they could evaluate nothing except by taste. Again, stimulations and destructive lesions of the cingulate gyrus,[10,11] of the prechiasmal and septal regions,[12] of the periaqueductal gray matter,[13] and of the amygdala[14,15] produced great changes in affect—diminished or abolished it—with tremendous changes in behavior. The ascending reticular activating system, outlined by Magoun and associates,[16] carries out what is surely the primary affective response, that of alertness. A vast amount of work on the hypothalamus has shown how dominant it is in the

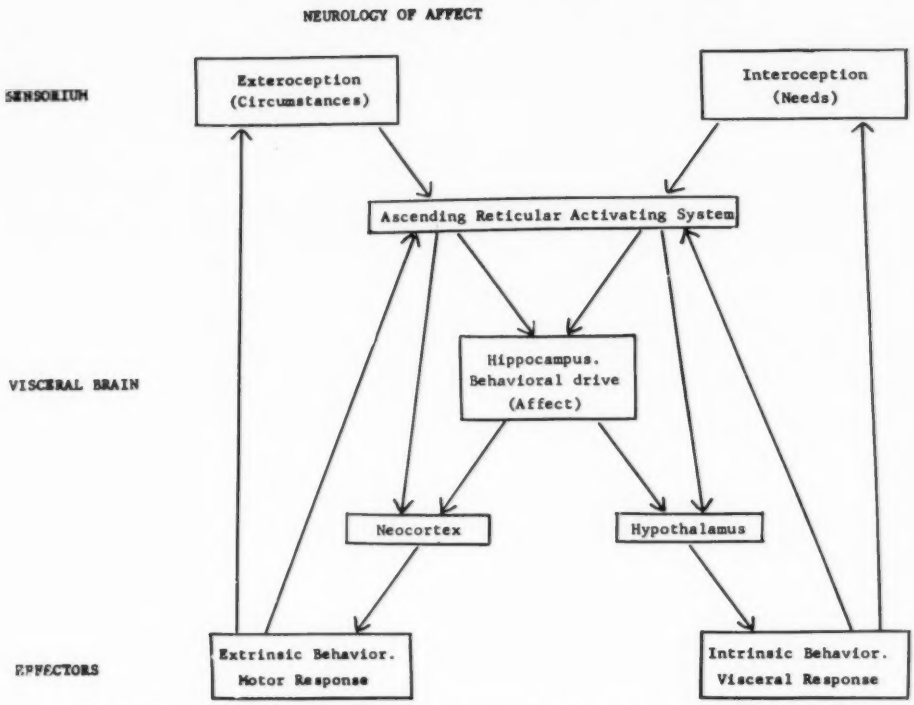

Fig. 3.—Diagram illustrating that both exteroceptive and interoceptive stimuli play upon the reticular activating system and visceral brain to produce extrinsic and intrinsic responses, with reciprocal control by feedbacks.

"alarm reaction"; the mechanisms of rage, hunger, sexual desire and feeling, and the activities of vasomotor control and sweating that characterize these states.

We may attempt to construct, as simply as possible, a scheme to illustrate the bare skeleton of the neurology of behavior. In Figure 3 are illustrated some of the foregoing points. Biological needs (interoception, e.g., hunger) act through the activating system and hippocampus and so stimulate behavioral drive (affect), which, through the neocortex, results in extrinsic behavior, such as the taking of food, and through the hypothalamus, in visceral response. Unconditional responses, such as this, lead to conditioned responses via exteroception, so that the sight of food in the presence of hunger may lead again through the activating system and hippocampus to taking food as the extrinsic response, and to the appropriate intrinsic, visceral response. Many feedbacks are possible, such as that whereby satisfaction lessens the need, reduces the behavioral drive (affect), and so ends the response. Many interrelationships cannot be illustrated in so simple a diagram. Figure 3 illustrates the idea that no information from the sensorium results in behavior without participation of affect or behavioral drive, as mediated through the visceral brain. Without pausing to discuss further these well-known mechanisms, we hasten on to mention a few clinical facts which illustrate the operation of these mechanisms in the neurology of affect.

Clinical Applications

Pharmacology and Motivation.—With the introduction of the so-called tranquilizing drugs, a new era of psychopharmacology

has begun. Not only do these drugs have a practical, clinical use, but they also provide a tool for the investigation of the functions of the areas of the brain which they particularly influence. They appear to influence chiefly the hypothalamus and the autonomic mediation of visceral accompaniments of affect. The two most familiar tranquilizing drugs, reserpine and chlorpromazine, both reduce the intensity of emotional states with relatively less impairment of intellectual functions than is observed in the case of the barbiturates, bromides, etc. As one would expect from these clinical effects, electrographic studies, as summarized by Himwich,[17] demonstrate that reserpine depresses the action of the posterior portion of the hypothalamus, thus reducing sympathetic activity (lowered heart rate and blood pressure, constriction of the pupils, increased intestinal motility). Chlorpromazine does nearly the same, but it also inhibits the sympathetic nervous system peripherally, and the parasympathetic system as well, so that it may cause the heart rate to increase. Both drugs stimulate the amygdala, the effect of which is to lessen the intensity of affect. Meprobamate, also a tranquilizer, evidently does not act on the amygdala, but seems to act on other parts of the rhinencephalon. Reserpine and chlorpromazine also depress the ascending reticular activating formation, as may be shown in electrograms taken from that structure in animals receiving those drugs. The emotional depression often seen when reserpine is used to reduce arterial hypertension is of more than passing interest.

Perhaps the most widely used of all drugs affecting human behavior is alcohol, and in this case the effect varies from one person to another but is in general the opposite of a tranquilizer. The effects of alcohol on the visceral brain have not been clearly defined, but its clinical effects in large doses suggest that it is a disinhibitor to the emotional circuits and a depressor of the reticular formation. Amphetamine in the experimental animal stimulates the ascending reticular formation and the cerebral cortex, as recorded electrographically, thus acting sympathicomimetically, while it alerts and produces euphoria in the human subject.

Disease and Motivation.—It would be most interesting to consider one neurologic disease after another, and, in the light of the neural mechanisms involved in behavior, to attempt to explain the effects of the disease on motivation. We shall mention only a select few, devoting our thought only to those which alter behavior *qualitatively*, i.e., in its *motivation*, in its affectively established values. It will be recalled from what has been said above that motivation, as affective attitude, is correlated with a complex balance of many drives, which in the aggregate constitute the person's character. Now, disease of the brain may alter this subtle balance, so that character is altered.

General paresis (dementia paralytica) notoriously changes the patient's personality, and the earliest psychiatric signs of this disease may be this subtle change in affect—from the meticulous to the slovenly, from the compliant to the aggressive, from the economical to the extravagant. The pathological changes in general paresis are found in all parts of the brain, but predominantly in the frontal and temporal lobes, where the destructive processes not only reduce the intellectual precision of the patient but upset the affective balance which previously set the values and goals of the personality. If we knew enough of the original mechanisms present before disease and had the patience to decipher under the microscope the pattern of disorder imposed by disease, we should be able to explain the psychotic behavior of the paretic in neurophysiological terms.

Frontal lobotomy is a much simpler insult to the brain, and produces changes in the personality which are rather well known and can be explained in terms of the systems destroyed. The chief effect of frontal lobotomy is the blunting of affective re-

actions and, in particular, motivation. This appears to be due to the interruption of the pathways between frontal cortex and thalamus. The connections of the cingulate gyrus and the septal regions must be important here.

The derangements of personality seen in temporal epilepsy must be our last example. The lesions responsible for this remarkable disorder are most frequently found in the anterior and medial aspects of the temporal lobe, that is, in the region of the amygdala, uncus, hippocampal gyrus, and hippocampus. The seizures include strange affective states, often a feeling of familiarity (déjà vu), bits of inappropriate behavior, which, as though they were a sort of motor hallucination, seem to arise from somewhere within the organism. Furthermore, the patients often exhibit a strange disorder of personality between seizures—unpredictable, unreliable, inconstant, and explosive reactions, with great alterations in affect and motivation. The hallucinatory states so often observed in these attacks, not only olfactory but also auditory or visual, may in themselves produce gross aberrations of behavior. It seems obvious that the pathological disorder in this portion of the visceral brain or in its environs not only produces the seizures but so disturbs the patient's affect (behavioral drive) as to modify his total behavior both episodically and between the episodes. Again, stimulation of the temporal lobes in these patients produces affective states, hallucinations, and a feeling of familiarity or "reminiscence," suggesting that these areas are important in memory. Finally, the drugs chlorpromazine and reserpine, discussed above, which alter affect by action on the hypothalamus, may, in excess, produce convulsions. All these observations add to the evidence that these structures play a leading part in the affective dynamics, and hence in the motivation, of behavior.

Summary

An analysis of the neurology of motivation involves us at once in the problem of human free will in a deterministic science. In view of the indispensable value of the sense of free will to the human personality, this dilemma is inescapable.

It is considered that motivation is identical with affect or desire, positive or negative, and is the subjective correlate of neuronal activity under the biological drive of original and acquired needs. These needs, at first primal and unconditioned, are elaborated by the addition of derivative and conditioned needs under the impact of experience. Thus, in a world of varying circumstances, conflicting needs lead to conflicting drives toward alternative actions and offer the organism a "choice," the resolution of which is accomplished when neuronal activity follows preponderant habitual paths.

"Free will" becomes the subjective experience of the resolution of conflict between biological drives. Whenever conflicts of drive are resolved, the sense of free will will reward the subject. This sense of free will, the inevitable accompaniment of the resolution of behavioral conflict, in no way contravenes deterministic causality in behavior, but constitutes a precious subjective value for the individual.

The neurologic mechanisms whose activity is associated with motivation or affect are largely found in the so-called visceral brain. Their activity is expressed through both visceral and extrinsic motor effectors. Hormonal and enzymatic effectors aid in the expression.

Experimental work and clinical disease demonstrate the importance of these neurovisceral mechanisms in behavioral drive, which is to say, in motivation.

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Some Properties of Brain Copper-Proteins in Hepatolenticular Degeneration

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This paper describes some properties of copper-protein combinations present in brains of patients with hepatolenticular degeneration and compares them with the properties of both naturally occurring and artificially created combinations of copper with proteins from normal human brain.

Hepatolenticular degeneration is characterized by a number of manifestations of abnormal copper metabolism.[1] In particular, the marked increase in brain copper content [2,3] and the improvement in neurological symptoms in some cases following administration of dimercaprol U. S. P. (BAL)[4-10] suggest that the accumulation of copper in the brain may be the primary factor in the production of the central nervous system dysfunction. This concept of the pathogenesis of the disease, together with evidence that copper is also essential for normal nervous tissue function,[11] has prompted us to investigate the types of organic combination in which copper is present in brains from cases of hepatolenticular degeneration and in normal brain. Three different copper-containing fractions have been separated under copper-free conditions from both normal brain and brains from cases of hepatolenticular degeneration.[12] In the latter, more than two-thirds of the pathological copper was found in Fraction I, which is obtained by extraction of the fresh tissue with acetate buffer pH 4.5 or with water or with bicarbonate buffer pH 8.2. This copper was quantitatively undialyzable at pH 8.2 and is presumably bound to proteins. Cerebrocuprein I, an essentially homogeneous brain protein containing 0.3% copper,[13] has been isolated both from bovine Fraction I and from normal human brain,[14] and shown to bind its copper in a form which does not react directly with sodium diethyldithiocarbamate.[15]

Some of the characteristics of copper-protein combinations from brains of cases of hepatolenticular degeneration have been discussed in a preliminary report.[16] The results described in more detail here, on the basis of additional pathological material, include observations on (1) the effect of pH on the dialyzability of Fraction I copper, (2) the capacity of Fraction I brain proteins to bind extraneous copper, (3) the capacity of Fraction I copper to react directly with sodium diethyldithiocarbamate, and (4) electrophoretic mobility.

Methods and Material

Precautions to avoid contamination with extraneous copper, the general conditions of fractionation procedures, criteria for selection of normal human brains for fractionation, the technique of preparative paper electrophoresis on Whatman No. 3MM paper, and the methods used for tissue homogenization, for copper analyses, and for determination of direct-reacting copper were all identical with those employed in previous work.[12-15] All fractionation procedures were carried out in cold rooms, either at about 4 C, during manipulation of aqueous solutions, or at about −13 C, during manipulation of aqueous-organic solvent mixtures. The pH of all buffer solutions

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was measured on a Beckman Model H-2 pH meter. All paper electrophoreses were run in copper-free barbital buffer pH 8.6, ionic strength 0.1, at 250 volts for 16 hours at 4 C. Paper strips were stained for protein with naphthol blue black. The Teflon plugs used to support the filter paper while eluting protein after preparative paper electrophoresis had a screw-threaded central opening, into which a threaded nylon rod could be inserted to permit easy removal of the plug from the conical centrifuge tube without contact with metal.

Fraction I was prepared from whole brain both as pH 4.5 acetate buffer extracts of the tissue and as water or pH 8.2 bicarbonate buffer extracts of the tissue, using the techniques previously described.[12] Four milliliters of buffer or water per gram of frozen tissue was used for all extractions. In order to obtain clear water or pH 8.2 buffer extracts, high speed centrifugation was necessary, and these extracts were centrifuged at 44,000 g in a Spinco Model L preparative ultracentrifuge. Free copper was removed from the metal centrifuge tube caps used in this apparatus by soaking in 0.5% sodium diethyldithiocarbamate solution, followed by exhaustive rinsing with methyl alcohol, and then with redistilled water.

The brains from Cases A and B of hepatolenticular degeneration, described previously,[12] had been stored at —15 C for about one month prior to the dialysis experiments and for about two years as frozen whole brain (Case A) or as lyophilized, dialyzed bicarbonate buffer extract (Case B) prior to the direct-reaction and electrophoresis experiments. Material from Cases C* and D† was frozen immediately after autopsy, and processing was begun within 72 hours of death in Case C and within one month of death in Case D. Patient C, aged 19, was in an advanced stage of the disease, with well-marked Kayser-Fleischer rings, and had been completely disabled by neurological deficit for two and one-half years. Patient D, aged 11 years at the time of death, from massive gastrointestinal hemorrhage, was in an early stage of the disease, with Kayser-Fleischer rings noted only on slit-lamp examination and with only minimal abnormalities on neurological examination. Both Cases C and D showed markedly low plasma ceruloplasmin values, as judged by the levels of indirect-reacting plasma copper found, which amounted to 48.2μg. % in Case C and to less than 10μg. % in Case D, as compared with a normal average of 112μg. %.

* Made available through the courtesy of Dr. Kenneth Keill.

† Made available through the courtesy of Dr. H. E. MacMahon.

Results

The total copper content of whole brain was 46.9μg. per gram of fresh tissue in Case C and 27.3μg. per gram of fresh tissue in Case D, as compared with an average of 4.1μg. per gram of fresh tissue in normal human brain. In agreement with the previously reported findings in Cases A and B,[12] more than two-thirds of the pathological copper in the brains from Cases C and D was extracted in Fraction I, and the amounts of copper obtained in Fraction I by extracting the fresh tissue with acetate buffer pH 4.5 and with bicarbonate buffer pH 8.2 were similar, amounting, respectively, per gram of fresh tissue to 34.3μg. and 36.6μg. in Case C and 18.9μg. and 18.6μg. in Case D. In Case C Fraction I was prepared also by extracting the tissue with redistilled water, the copper content of 35.8μg. per gram of fresh tissue found in this extract being in good agreement with the values obtained with the buffer extractions.

Effect of pH on Dialyzability of Fraction I Copper.—The effect of the pH on the dialyzability of Fraction I copper from brains of cases of hepatolenticular degeneration was investigated in the following manner: Aliquots of pH 8.2 bicarbonate buffer extracts, water extracts, or pH 4.5 acetate buffer extracts of the tissue, containing about 20μg. of original tissue copper, were each subjected to equilibrium dialysis against single 50-vol. portions of bicarbonate, acetate, or citrate buffers of ionic strength 0.1 for 72 hours, with frequent shaking during each day. The individual experiments carried out are indicated in Figure 1, which shows the amounts of copper bound at different pH's expressed as percentages of the copper present in the original extract before dialysis. After dialysis, the pH of the external solutions‡ and the copper in the external, as well as in the

‡ For technical reasons, it was considered inadvisable to measure the pH of the internal solutions directly. With buffers of this ionic strength, the pH of the solution inside the bag may be assumed to have equaled that of the external solution.

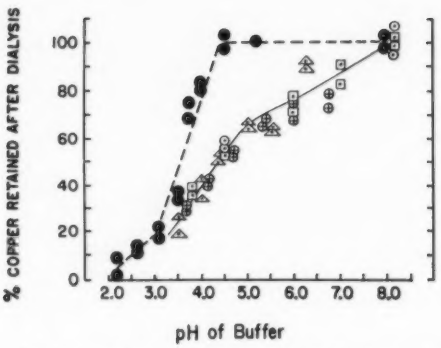

Fig. 1.—Effect of pH on the dialyzability of Fraction I copper from brains of cases of hepatolenticular degeneration and from the normal human brain.

In this Figure, solid black circles indicate normal human brain: pH 8.2 extract dialyzed at pH 8.2; pH 5.2 extract dialyzed at pH 5.2; pH 4.5 extract dialyzed against water and then against buffers of pH 4.5 or below. Clear circles, clear squares, triangles, and circles with cross represent, respectively, four cases of hepatolenticular degeneration. Clear circles represents Case A: pH 8.2 extract dialyzed at pH 8.2; pH 4.5 extract dialyzed at pH 4.5. Squares represent Case B: pH 8.2 extract dialyzed at pH 8.2; pH 8.2 extract dialyzed against water and then against buffers of lower pH; pH 4.5 extract dialyzed at pH 4.5. Triangles represent Case C: water extract dialyzed against buffers of lower pH. Circles with cross represent Case D: pH 8.2 extract dialyzed against water and then against buffers of lower pH; pH 4.5 extract dialyzed at pH 4.5 and below. All external buffers, ionic strength 0.1; at pH 8.2, sodium bicarbonate buffer; pH 7.0 to 3.5, sodium acetate buffers; pH below 3.5, citrate-NaOH-HCl buffers.

internal, solutions were measured, and the copper bound at each pH was calculated by subtracting the amount of copper in an equivalent volume of the external solution from the total copper inside the dialysis bag.

In Fraction I from normal human brain, numerous experiments have established the essential absence of copper loss on dialysis at pH 4.5. In Fraction I from the brains of all four cases of hepatolenticular degeneration thus far investigated, on the other hand, about 40% of the copper was lost on dialysis under similar conditions. As illustrated in Figure 1, in Fraction I from normal human brain, most of the loss of copper on dialysis occurred in a steep decline in the proportion of retained copper at pH's between 4.0 and 3.0. In Fraction I from the brains of cases of hepatolenticular degeneration, in contrast, there was a much more gradual loss of copper over a much wider pH range.

Capacity of Fraction I Brain Proteins to Bind Extraneous Copper.—In measuring the capacity of Fraction I brain proteins to bind extraneous copper during dialysis against copper-containing solutions, it seemed desirable to keep the copper concentration in the external solutions at a level not exceeding the total copper concentration of normal plasma. All dialyses were therefore carried out against external solutions containing 1μg. of copper per milliliter as $CuSO_4$ added to sodium acetate buffer pH 7.2, ionic strength 0.1. Aliquots of pH 8.2 bicarbonate buffer extracts, corresponding to about 1 gm. of fresh tissue, were dialyzed against 50 vol. of redistilled water for 24 hours and then dialyzed for 72 hours against single portions of the copper-containing sodium acetate solution, the volume of which was so adjusted that the total amount of copper in the external solution equaled approximately 50μg. per gram of fresh tissue represented inside the dialysis bag. After dialysis, the copper in the external and in the internal solutions was measured, and the extraneous copper bound was calculated as the total copper inside the dialysis bag minus the sum of the original tissue copper plus the amount of copper in an equivalent volume of the external solution.

Under these conditions, Fraction I proteins from three different normal human brains bound 17.3μg., 31.7μg., and 34.5μg. of extraneous copper per gram of fresh tissue. Cases A, C, and D of hepatolenticular degeneration bound, respectively, 16.9μg., 8.8μg., and 25.2μg. of extraneous copper per gram of fresh tissue. In Case D dialysis was also carried out against volumes of copper-containing sodium acetate solution corresponding to 350μg. of external copper per gram of fresh tissue. The extraneous copper bound was 124μg. per gram of fresh tissue, as compared with 135μg. per gram

of fresh tissue bound by material from normal human brain under the same conditions. Fraction I proteins from both normal human brain and brains of cases of hepatolenticular degeneration are thus capable of binding extraneous copper to reach copper concentrations up to 50 times those present in Fraction I in normal human brain. In no instance did the amount of extraneous copper bound by Fraction I proteins from brains of cases of hepatolenticular degeneration exceed the amount of extraneous copper bound by the control material from normal human brain processed at the same time.

Capacity of Fraction I Copper to React Directly with Sodium Diethyldithiocarbamate.—In order to obtain the concentration of tissue copper required in the method employed for the determination of direct-reacting copper,[15] copper-proteins in pH 8.2 and pH 4.5 extracts of normal human brain were concentrated by precipitation with 3 vol. of acetone at −13 C, and the copper-protein in the precipitates was dissolved in sufficient 0.2 M ammonium bicarbonate to make a solution containing 5% to 10% protein. The pH 8.2 extracts from the cases of hepatolenticular degeneration were analyzed without previous acetone precipitation. The pH 4.5 extracts both from normal human brain and from the brains of cases of hepatolenticular degeneration were dialyzed against a single 70-vol. portion of redistilled water for 64 hours, with constant mechanical shaking prior to acetone precipitation, as above.

The extent to which Fraction I copper from normal human brain and from brains of cases of hepatolenticular degeneration was found to react directly with sodium diethyldithiocarbamate is shown in the accompanying Table. Less than 15% of the copper in the material from normal human brains reacted directly with carbamate. In contrast, of extraneous copper bound by proteins in pH 8.2 extracts of normal human brain after dialysis against solutions containing added copper, 99% reacted directly.[15] Less than 10% of the tissue copper in pH 8.2 extracts from Cases C and D of hepatolenticular degeneration reacted

Direct Reaction of Copper in Fraction I Brain Copper-Proteins with Sodium Diethyldithiocarbamate

Preparation	Cu in Sample Analyzed, μg.	Extent of Direct Reaction	
		Cu, μg.	As Per Cent of Total Cu in Sample
Normal human Fraction I			
As pH 4.5 extract *	11.80	1.45	12
	9.74	1.06	11
Pure human cerebrocuprein I (isolated from pH 4.5 extract)	5.25	0.27	5
	6.39	0.18	3
As pH 8.2 extract	8.37	0.91	11
	4.62	0.35	8
PH 8.2 extract	23.60	20.50	99 ‡
Dialyzed *vs.* added Cu †	24.50	21.30	99 ‡
Hepatolenticular degeneration Fraction I			
As pH 8.2 extract (Case C)	7.37	0.48	7
	14.86	0.95	6
As pH 8.2 extract (Case D)	7.62	0.15	2
	7.50	0.13	2
As pH 4.5 extract (Case C) *	10.97	4.18	38
	10.12	4.18	41
As ph 4.5 extract (Case D) *	9.06	1.53	17
	9.12	1.55	17
Liver, pH 8.2 extract (Case C)	9.06	0.40	4
	16.61	0.43	3

* Dialyzed at pH 4.5.

† The samples placed in the spectrophotometer cuvettes in these experiments contained smaller amounts of brain proteins, and hence smaller amounts of tissue copper, than the samples employed for the measurement of direct-reacting tissue copper in pH 8.2 extracts, which are illustrated on the lines immediately above.

‡ Per cent of added Cu reacting directly.

directly with carbamate. Copper in a pH 8.2 extract of liver obtained as a biopsy specimen from Case C also failed to react directly to a significant degree.

After dialysis of pH 4.5 extracts from Cases C and D of hepatolenticular degeneration, 17% to 41% of the retained copper appeared to react directly. In the analyzed material from Case C, however, in which a single, relatively large-scale dialysis (95 ml. of pH 4.5 extract dialyzed against about 7 liters of water) had been employed, the copper loss on dialysis begun at pH 4.5 was not as great as that demonstrated on dialysis in triplicate of small aliquots from pH 4.5 extracts. The copper loss in the latter was in agreement with the findings shown in Figure 1 for the water extract from this brain dialyzed against buffers of pH 4.5. Much of the direct-reacting copper in the material from the pH 4.5 extract from Case C, therefore, appeared to represent either contamination with extraneous copper or retention of some of the copper demonstrable in other experiments to be dialyzable at pH 4.5. The proportion of Fraction I copper from brains of cases of hepatolenticular degeneration which resembled normal Fraction I copper in being both undialyzable at pH 4.5 and indirect-reacting after such dialysis was estimated as 44% in Case C and as 47% in Case D.

Electrophoretic Mobility. — Copper-proteins in pH 8.2 extracts and in dialyzed pH 4.5 extracts of normal human brain and of brains from cases of hepatolenticular degeneration were concentrated by acetone precipitation and solution in 0.2 M ammonium bicarbonate, as described in the preceding section. Preparative paper electrophoresis was then carried out, as previously described.[13,14] Four-tenths milliliter of protein solution was applied to each 6-cm.-wide strip of Whatman No. 3MM paper, each preparative run including two or three such strips. Since pH 8.2 extracts of the tissue contained about four times as much protein as did pH 4.5 extracts, the amount of fresh tissue represented in the concentrated protein solutions applied to the papers in each run varied from about 3 gm., in the case of material from pH 8.2 extracts of the tissue, up to about 16 gm., in the case of material from pH 4.5 extracts of the tissue. After electrophoresis, the paper strips were cut into transverse bands of 1 cm. length. Bands of corresponding mobility were pooled and their protein eluted by centrifugation, followed by washing the papers in each tube three times with barbital buffer, as previously described.[13,14] The eluate from each set of pooled bands was analyzed for total copper and for direct-reacting copper. Each electrophoresis run also included an aliquot of the brain protein solution and a sample of plasma on paper strips 2 cm. wide which were stained for protein. Preliminary studies in which eluted copper was measured over a mobility range of −12 cm. to +18 cm. established that in material from hepatolenticular degeneration, under the conditions employed, significant amounts of copper were not found outside the 0 to +12 cm. mobility range. The sum total of copper in all the eluted fractions after electrophoresis ranged from 68% to 90% of the copper in the material placed on the paper. In calculating the eluted copper as micrograms per gram fresh tissue, correction was made for this known copper loss during electrophoresis and elution.

The results of electrophoresis of material from dialyzed pH 4.5 extracts of the tissue are shown in Figure 2. Paper strips stained for protein showed at least five bands, indicating that at least five different protein components were present in the solutions from the pH 4.5 extracts. In material from three normal human brains, the main peak of copper was found reproducibly at a mobility of +4 to +5 cm., most nearly approximating, although slightly less than, the mobility of a plasma α_2-globulin. The smaller copper peak, at +9 to +10 cm., corresponding to the mobility of plasma albumin, was variable in height but in these experiments showed no direct-reacting cop-

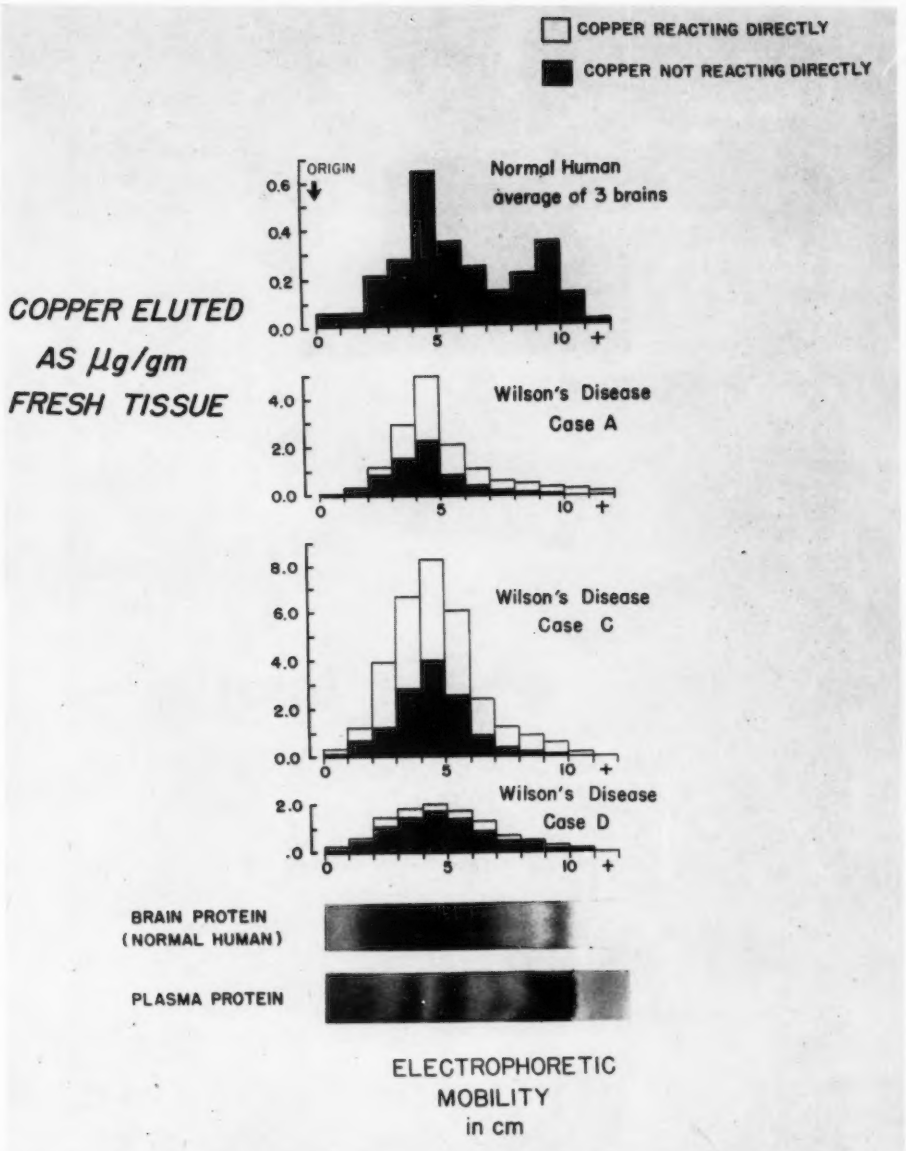

Fig. 2.—Copper eluted and protein stained after electrophoresis of material from dialyzed pH 4.5 extracts of normal human brains and of brains of cases of hepatolenticular degeneration. Clear rectangles represent copper reacting directly with sodium diethyldithiocarbamate; black rectangles, copper not reacting directly. The scale representing copper eluted from the material from normal human brains is tenfold that shown for the copper eluted from the material from the brains of the cases of hepatolenticular degeneration.

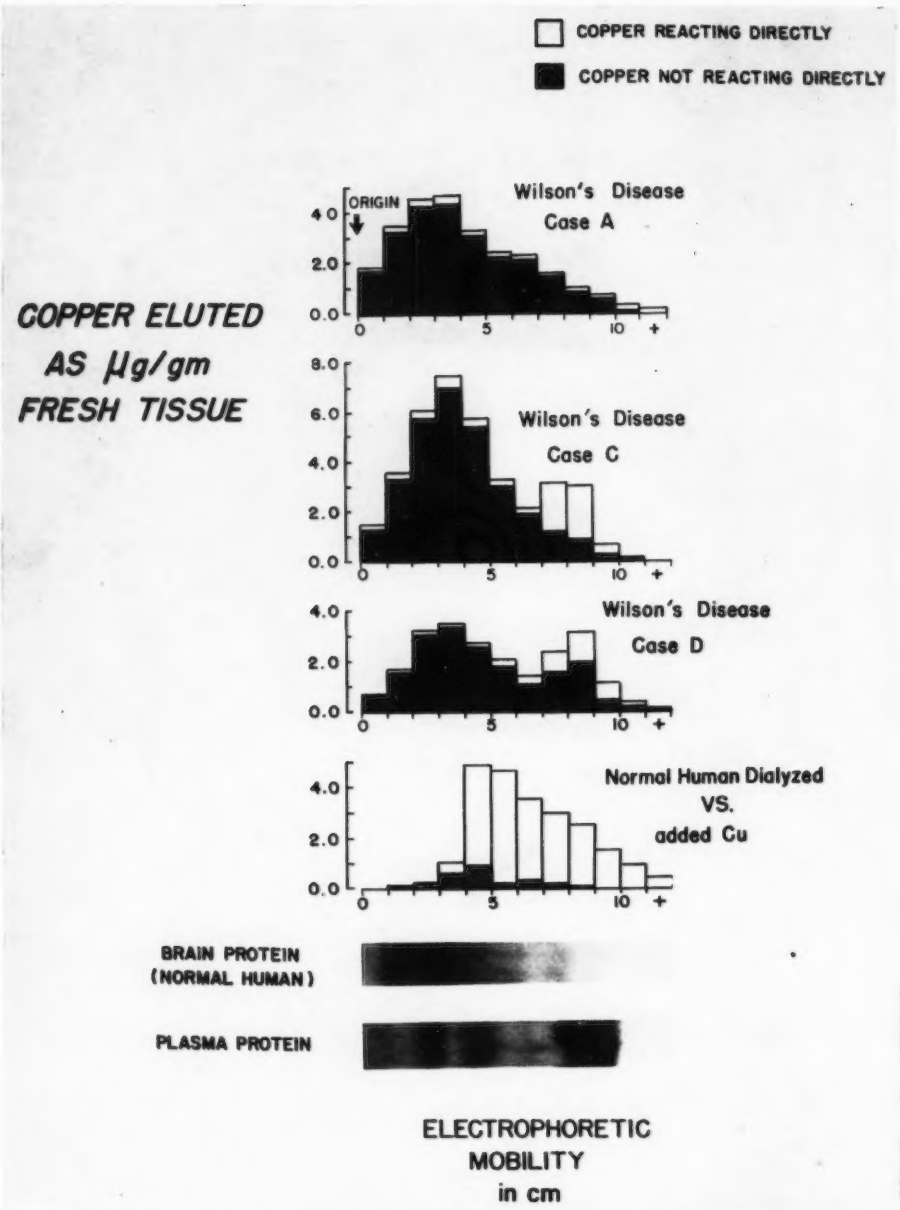

Fig. 3.—Copper eluted and protein stained after electrophoresis of material from pH 8.2 extracts of brains of cases of hepatolenticular degeneration and from pH 8.2 extracts of normal human brain after dialysis against solutions containing added copper. Clear rectangles represent copper reacting directly with sodium diethyldithiocarbamate; black rectangles, copper not reacting directly.

per. When extraneous copper (in amounts up to 5.9μg. per gram of fresh tissue represented) was added by dialysis to material from pH 4.5 extracts of normal human brain, the bulk of the direct-reacting added copper bound was found at a mobility of +4 to +5 cm., identical with the mobility shown by the indirect-reacting original tissue copper in this and in other experiments.

In the three cases of hepatolenticular degeneration, the indirect-reacting copper in material from dialyzed pH 4.5 extracts showed a peak at a mobility similar to that of the major copper peak in the material from the three normal human brains. As indicated in the preceding section and in the accompanying "Comment," some of the direct-reacting copper shown at this mobility in material from dialyzed pH 4.5 extracts from Cases A and C probably represents artifact.

Figure 3 shows the results of electrophoresis of material from pH 8.2 extracts. In the three cases of hepatolenticular degeneration, the copper in this material, representing the total Fraction I copper from these pathological brains, rather than only that portion of Fraction I copper stable to dialysis at pH 4.5, was found spread over a relatively wide range of mobilities. Some of the differences in copper-protein mobility found between the material from pH 8.2 extracts and the material from pH 4.5 extracts of these pathological brains may possibly be related to marked differences in the protein composition of the solutions applied to the paper, since the material from the pH 8.2 extracts contained, in addition to the Fraction I copper-proteins, much protein insoluble in the pH 4.5 extracts. Nevertheless, it is noteworthy that in all three cases of hepatolenticular degeneration investigated in this respect, the peak of copper in material from pH 8.2 extracts was found at a mobility of +3 to +4 cm., as compared with the peak at +4 to +5 cm. in the material from pH 4.5 extracts; and much larger amounts of copper were found at mobilities of +2 to +3 cm. and +1 to +2 cm. In hepatolenticular degeneration a considerable portion of the total Fraction I copper was thus found at mobilities similar to those of plasma β-globulins.

Figure 3 also illustrates the behavior of copper added to material from pH 8.2 extracts of normal human brain by dialysis against buffer containing added copper in a copper concentration less than that of the brain protein solution. In the illustrated experiment, a concentrated brain protein solution containing 9.7μg. of original tissue copper per milliliter was dialyzed against 80 vol. of pH 7.2 sodium acetate buffer containing 4μg. of added copper per milliliter. After dialysis, the copper concentration inside the dialysis bag was 14 times that of the external solution, and the normal brain proteins had bound extraneous copper to reach a proportion of copper to protein seven times that of the original Fraction I extract. In contrast to the pathological copper of hepatolenticular degeneration, this copper bound in vitro by normal brain proteins not only reacted directly with carbamate but also was not found in appreciable quantities at mobilities similar to those of plasma β-globulins, although proteins with these mobilities appeared to make up one-half or more of the total proteins in the electrophoresis material. The absence of significant amounts of bound extraneous copper in the mobility range of 0 to +4 cm. was confirmed after preparative paper electrophoresis of material from a pH 8.2 extract of another normal human brain after a similar dialysis against added copper. The peak of the small proportion of indirect-reacting original tissue copper was found at the same mobility as in the material from the pH 4.5 extracts, most nearly approximating the mobility of a plasma α_2-globulin.

Comment and Conclusions

In all four brains from cases of hepatolenticular degeneration thus far investigated, more than two-thirds of the

pathological brain copper has been extracted in Fraction I. The loss of about 40% of Fraction I copper from the brains of two cases of hepatolenticular degeneration (Cases A and B of the present paper) on dialysis at pH 4.5, as opposed to the ability of Fraction I from normal human brains to retain essentially all of its copper under similar conditions, was described in a previous report.[12] In the case of normal human brain, most of the loss of copper on dialysis of Fraction I extracts has been found to occur in a steep decline in the proportion of retained copper between pH 4.0 and 3.0. The experimental points are, in fact, in reasonably good agreement with the theoretical hydrogen-ion dissociation curve calculated from the Henderson-Hasselbalch equation for an acidic group with a pK of 3.5. These results cannot be directly interpreted as indicating that Fraction I copper from normal human brain is bound to a group having a pK of about 3.5 for hydrogen-ion dissociation in view of the complicating effects of competition between copper and hydrogen ions for the anionic group of the protein[17] and the possible effect of the metal on the pK for hydrogen-ion dissociation of the group to which it is bound.[18] The data obtained do suggest, however, first, that Fraction I copper from normal human brain may all be bound to protein through a single type of group and, second, that this group may be one having a relatively low pK for hydrogen-ion dissociation. A previous report[13] has commented upon the evidence suggesting that in cerebrocuprein I, the purified copper-protein isolated from normal brain, the copper may possibly be bound to the protein through carboxyl groups. In contrast, the finding in Cases C and D of hepatolenticular degeneration that more than 40% of the copper in Fraction I extracts was lost on dialysis at pH 4.5 confirms the results previously reported[12] in Cases A and B and provides additional data supporting the previous conclusion that in brains from cases of hepatolenticular degeneration a significant portion of the pathological brain copper is bound to protein through linkages more labile to acid pH than the copper-protein bonds in Fraction I from normal human brain. Furthermore, the gradual loss of Fraction I copper from brains of cases of hepatolenticular degeneration over a relatively wide pH range suggests that in hepatolenticular degeneration the pathological copper is bound to protein through more than one type of linkage.

Less than 15% of the copper in Fraction I from normal human brains, obtained as pH 8.2 extracts of the tissue, as dialyzed pH 4.5 extracts of the tissue, or as purified human cerebrocuprein I[14] isolated from pH 4.5 extracts of the tissue, reacted directly with sodium diethyldithiocarbamate. In contrast, 99% of extraneous copper bound to proteins in pH 8.2 extracts from normal human brain after dialysis against solutions containing added copper reacted directly with this reagent.[15] In Cases C and D of hepatolenticular degeneration, less than 10% of the Fraction I copper in pH 8.2 extracts was found to react directly with carbamate. This finding differs from the previously reported[15] results in Cases A and B of hepatolenticular degeneration in which, after prolonged storage, 29% to 45% of the copper in pH 8.2 extracts had been found to react directly. The control material in the previous study had included material from a brain in which 17 hours elapsed between death and autopsy and in which the brain was stored frozen for more than six months prior to analysis without demonstrable effect of these conditions on the capacity of Fraction I brain copper to react directly. Nevertheless, the present results on the fresher material from Cases C and D suggest that the previously observed values in Cases A and B were the result of postmortem change or other artifact. The present results indicate that Fraction I copper in pH 8.2 extracts from relatively fresh brains of cases of hepatolenticular degeneration, like that in normal human brain, does not react directly with carbamate to a sig-

nificant degree. The copper-protein bonds occurring in the brain in cases of hepatolenticular degeneration, although more labile to acid pH than the copper-protein bonds of naturally occurring copper proteins from normal human brain, thus appear to be of a less labile type than the copper-protein bonds artificially produced by addition of copper to normal brain proteins in vitro. Copper in a pH 8.2 extract of liver obtained as a biopsy specimen from Case C also failed to react directly with carbamate to a significant degree. The capacity of the copper in the liver of cases of hepatolenticular degeneration to react directly with copper-binding agents employed in histochemical studies[19,20] may be attributed in part to the probable denaturation of tissue proteins by contact with formalin or ethanol at room temperature. The proportion of copper in Fraction I from brains of cases of hepatolenticular degeneration which resembled Fraction I copper from normal human brains in being both undialyzable at pH 4.5 and indirect-reacting with carbamate after such dialysis was estimated as about 45% of the total Fraction I copper from the pathological brains.

On preparative paper electrophoresis of material from dialyzed pH 4.5 extracts of normal human brains, the main peak of copper was found reproducibly at a mobility most nearly approximating, but slightly less than, that of a plasma α_2-globulin. A second copper peak was found at a mobility similar to that of plasma albumin, but the height of this second copper peak was markedly variable in material from different normal human brains, and it is considered probable that the occurrence of much copper at this mobility is attributable chiefly to protein breakdown.[14] On preparative paper electrophoresis of material from dialyzed pH 4.5 extracts from the brains of cases of hepatolenticular degeneration, the peak of the copper which remained undialyzable at pH 4.5 and indirect-reacting with carbamate after such dialysis was found at a mobility identical with that shown by the major peak of copper in material from normal human brains. This copper thus represents copper in the brains of cases of hepatolenticular degeneration which has not been demonstrated to be bound in a form different from Fraction I copper in normal human brains. With allowance for protein overlap onto the 1 cm. bands immediately adjacent to the peak band, such copper might amount to about 20% or more of the total Fraction I copper from the pathological brains. The amounts of cerebrocuprein I, the purified copper protein isolated from normal human Fraction I,[14] which are present in the brains of cases of hepatolenticular degeneration have not yet been determined.

Copper in material from pH 8.2 extracts from the brains of cases of hepatolenticular degeneration, representing total Fraction I copper from these brains, rather than only that portion of Fraction I copper which was stable to dialysis at pH 4.5, was found spread over a relatively wide range of electrophoretic mobilities. This finding suggests that in hepatolenticular degeneration the total Fraction I copper is bound to a number of different proteins. In particular, a considerable portion of the copper in this material appeared to be bound to proteins having electrophoretic mobilities at pH 8.6 similar to those of plasma β-globulins, whereas the copper in material from normal human brains appeared to be bound chiefly to proteins with greater electrophoretic mobilities. Results of electrophoresis of material from pH 8.2 extracts of normal and pathological brains thus provide further evidence that in hepatolenticular degeneration a significant portion of the pathological brain copper is bound to proteins in a form different from that accounting for the bulk of the Fraction I copper in normal human brain.

Artificial copper-protein combinations could be produced in vitro by addition of extraneous copper to proteins from pH 8.2 extracts of normal human brains during dialysis against buffer containing added copper. These copper-protein combinations

differed from the abnormal copper-protein combinations formed in vivo during the course of hepatolenticular degeneration not only in their capacity to react directly with carbamate but also in their electrophoretic mobility. Thus, almost none of the copper added in vitro to normal brain proteins was found at mobilities corresponding to those of plasma β-globulins, whereas copper-protein combinations with such mobilities made up a major portion of the Fraction I copper in the brains from cases of hepatolenticular degeneration. The total amounts of extraneous copper bound by proteins in pH 8.2 extracts from normal human brain during dialysis against buffer containing added copper were found to equal, and indeed exceed, the amounts of extraneous copper bound by similar material from brains of cases of hepatolenticular degeneration. The present observations on brain, therefore, do not support the theory [21] that in hepatolenticular degeneration the tissues accumulate copper because they contain proteins with "an abnormal avidity" for extraneous copper.

Evidence has been presented that a significant portion of the pathological copper accumulating in the brain in hepatolenticular degeneration is bound to proteins in copper-protein combinations differing, both in electrophoretic mobility and in lability to acid pH, from those occurring in appreciable amounts in normal human brain. Although the abnormal copper-protein combinations found in these pathological brains do not resemble those produced by addition of copper to normal brain proteins in vitro, it is nevertheless possible that, with more intricate mechanisms for copper binding which may be present during life, much of the pathological copper in the brains of cases of hepatolenticular degeneration becomes bound to brain proteins which are normally copper free. The accumulated copper might then interfere with functions, such as enzymatic activity, of some normally copper-free protein(s) and thus lead to the neurological deficits occurring in this disease. If this hypothesis is correct, there are at least two possible mechanisms which might explain the observations that, although abnormalities in copper metabolism may be present from birth §, neurological symptoms may not appear until the age of 30 or more.[5] One might speculate that the pathological copper, even if bound to a single brain protein or distributed in a constant ratio between several brain proteins, must slowly accumulate to exceed a certain threshold before the function of the protein(s) is altered to a degree sufficient to produce manifest neurological deficit. Alternatively, it is possible that, during the course of the disease, additional increments of accumulating copper might be bound successively to different brain proteins having successively weaker affinities for the metal. Those copper-protein combinations formed predominantly at a relatively late stage in the disease might then have a more deleterious effect on normal cerebral metabolism than those copper-protein combinations formed early in the disease. The present data from Case D indicate that in hepatolenticular degeneration brain copper may be elevated to about seven times the normal levels in a patient showing only minimal neurological deficit. No evidence definitely supporting the second, alternative hypothesis above was provided by comparison of the data from the advanced Case (C) with the data from the early Case (D), since there was no definite indication that in the more advanced case a larger proportion of the pathological brain copper was bound in relatively labile form, i. e., to proteins having a weaker affinity for copper.

Summary

Properties of copper-protein combinations present in the brains of four cases of hepatolenticular degeneration are compared with the properties of both naturally occurring and artificially created combinations

§ The absence of detectable plasma ceruloplasmin in a 10-month-old infant sibling of a patient with Wilson's disease has been observed by Scheinberg.[22]

of copper with proteins from normal human brain.

1. The total Fraction I brain copper in hepatolenticular degeneration appears, on preparative paper electrophoresis, to be bound to a number of different proteins.

2. A significant portion of the pathological copper in the brains of cases of hepatolenticular degeneration appears to be bound to protein through linkages more labile to acid pH than the copper-protein bonds in Fraction I from normal human brain.

3. In hepatolenticular degeneration most of that portion of Fraction I copper which resembled normal human Fraction I copper, both in being undialyzable at pH 4.5 and in failing to react directly with sodium diethyldithiocarbamate after such dialysis, was also similar to normal human Fraction I copper in electrophoretic mobility. This copper may therefore prove to be in a form identical with one of those occurring in normal human brain.

4. Copper in pH 8.2 extracts of two brains and one liver biopsy specimen from cases of hepatolenticular degeneration did not react directly with sodium diethyldithiocarbamate to a significant degree, whereas 99% of copper added in vitro to proteins from similar extracts of normal human brain reacted directly. The copper-protein bonds occurring in hepatolenticular degeneration thus appear to be of a firmer type than those artificially produced by addition of extraneous copper to proteins from normal human brain.

5. Brain copper-proteins in hepatolenticular degeneration also differed from those produced by addition of copper to normal brain proteins in vitro in showing much copper bound to proteins with electrophoretic mobilities at pH 8.6 similar to those of plasma β-globulins, whereas almost none of the copper added to normal brain proteins was found at these mobilities.

6. The amounts of extraneous copper bound by proteins in pH 8.2 extracts from brains of cases of hepatolenticular degeneration during dialysis against solutions containing added copper did not exceed the amounts of copper bound by similar material from normal human brains under the same conditions.

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Augmentation of the Inflammatory Reaction by Activity of the Central Nervous System

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As an aspect of the continuing study in this laboratory of the participation of the nervous system in integrating appropriate and inappropriate adaptive reactions,[1] the inflammatory response has been of prime interest.

It was a Galenic dictum that any part of the body may influence any other part through neural connections. In the 18th century, Cullen, Pinel, and Baglivi held the view that disorders of the nervous system underlay most disease processes. This emphasis gave rise to the school of "systematic correlative neuropathologists," which dominated French concepts of disease in the first half of the 19th century.[2] In the latter half of the 19th century growing emphasis on localized cellular alterations overshadowed the earlier interest in generalized reactions.[3]

Cohnheim, in 1882,[4] inferred that vasomotor nerves played no part in inflammation, but by 1909 it was established (by the work of Samuel, Meltzer, and Meltzer, and of Roger, Adami, and others), as cited by Florey,[5] that interruption of sympathetic vasoconstrictor nerves led to vasodilatation and enhanced inflammatory reactions following noxious stimulation. On the other hand, interruption of vasodilator fibers resulted in constriction and diminished inflammation subsequent to injury. The latter procedure delayed elimination of injected micro-organisms and slowed recovery from injury.

Bruce, in 1910,[6] was among the first to suggest that an axon reflex was involved in the vasodilatation of inflammation. In the 1920's and 1930's several investigators studied the participation of the nervous system in the inflammatory process.[7-9] Sir Thomas Lewis[9] analyzed the "triple response" of the skin to injury and showed that a red central area surrounded by a brighter red flare appeared upon injuring the normal skin, but that if the sensory nerves to the skin had been cut five to seven days before the injury, only the central red area developed. If the injury occurred before the peripheral nerve fibers had degenerated, the surrounding flare was still evident. He regarded the central red area as being due to dilatation of venules and capillaries that had been acted upon directly by a chemical substance liberated by the injury tissue. This substance, termed H substance because of the similarity of its effects to those of histamine, was thought to stimulate afferent nerve endings in the injured area. In this way, an axon reflex was initiated that dilated arterioles outside the injured area and resulted in "flare." Recently, potent pharmacodynamic agents have been demonstrated to participate in inflammation.[10-17]

Previous studies from this laboratory have demonstrated that many of the organs

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of the body become more readily damaged during or after periods perceived as threatening: Vasodilatation, edema, diapedesis, hemorrhage, erosion, increased friability of tissue, lowered pain threshold, and impaired organ function have been observed in the skin,[18] nose,[19] airways,[19] stomach,[20] colon,[21] bladder,[22,23] vagina,[24] and the subcutaneous tissue of the scalp.[25] These changes could be induced rapidly by appropriate alteration of the environment, as by interviews which augmented or decreased the perception of threat.

The following section is a report concerning the pertinence of vasomotor influences and certain proteolytic enzymes and polypeptides released or accumulated not only when lower levels of the nervous system but also when the highest levels are involved in adaptive responses. The participation of various levels of activity of the nervous system in inflammation was analyzed through study of modifications of the inflammatory response to noxious stimulation associated with the axon reflex, the thermoregulatory reflexes, and suggestions during hypnosis.

I. Demonstration That the Inflammatory Response Can Be Modified by Neural Activity Integrated at the Segmental Level: the Axon Reflex

A. The pain threshold is lowered in the flare zone of the axon reflex.

Bilisoly, Goodell, and Wolff[26] observed that the pain threshold in the flare area of the axon reflex was lowered, as measured by the hair-pull method, by thermal dolorimetry, and by von Frey hairs. The axon reflex was studied as an example of the simplest integrative pattern that could be relevant to inflammation. Axon reflexes were induced on the volar surface of the arms by intradermal injection of 0.05 cc. of histamine phosphate (1:1,000) in six subjects. The lowered pain thresholds in the flare zones were demonstrated repeatedly in each subject.

B. The response to injury is heightened in zones of vasodilatation.

Bilisoly, Goodell, and Wolff[26] also used the axon-reflex flare to illuminate the relation between vasodilatation and heightened tissue vulnerability. Since the pain threshold was lowered during the period of active vasodilatation, it was suggested that an added standard noxious stimulation would have a more damaging effect within such an area than in control areas. Hence, axon-reflex flares were induced on the volar surface of one arm, and the other arm served as a control. It was then shown that, as the result of exposure to similar intensities of noxious thermal or chemical stimulation, there was significantly more skin damage in the zone of flare on the one arm than in comparable areas on the control arm. These differences were most striking 48 hours after thermal injuries.

C. Protease and bradykinin-type polypeptides are increased in amount in subcutaneous perfusate collected from the flare zone of the axon reflex.

Previous studies of blister fluid by Armstrong, Keele, and associates[15] and of the subcutaneous fluid collected from the scalp during vascular headache of the migraine type by Ostfeld et al.[25] indicated that this tissue fluid contained increased amounts of substances resembling polypeptides of the bradykinin type, as defined by Rocha e Silva et al.[27] Hence experiments were devised that permitted the collection of a subcutaneous perfusate from the zone of axon-reflex flare induced by injuring the skin by intracutaneous histamine phosphate at least 4 cm. distal to the site of fluid collection. In other instances the skin was damaged by heat or by cooling with ice.

Subjects and Method:

The subjects studied were two healthy adults and three patients: One man had had a gunshot injury of the brachial plexus, with absence of sensation in the region stimulated and perfused; one woman had absence of sympathetic innervation of the forearm, as a sequel of sympathectomy, and a second woman had "cold allergy"; i.e., she readily developed urticaria in response to cold stimulation.

The method of perfusing the subcutaneous space is a modification of that of Fox and Hilton.[28]

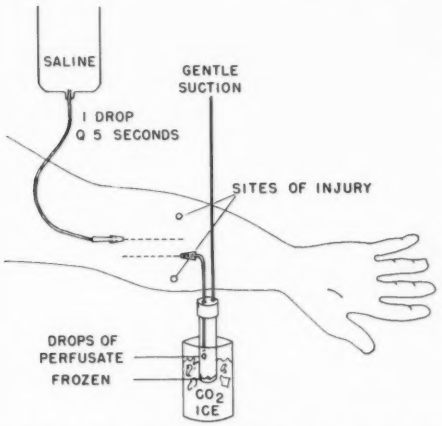

Fig. 1.—The arm prepared for perfusion and immediate freezing of perfusate as collected. Two No. 20, 2-in.-long perforate needles were inserted into the subcutaneous spaces parallel to each other and at a distance of approximately 1.5 cm. apart. This method is an adaptation of that of Fox and Hilton.

Figure 1 shows the method of inflow and outflow, using perforate needles. These needles were No. 20 steel hypodermic needles with eight perforations in the shafts.* The needles were inserted into the subcutaneous space of the volar surface of the forearm parallel to each other and approximately 1.5 cm. apart. The rate of inflow of the perfusion fluid (isotonic saline) was 0.5 cc. a minute. The perfusate was collected in siliconized tubes and was immediately assayed or frozen in CO_2 snow to prevent alteration and subsequently assayed when convenient. The perfusate was assayed by the conventional smooth muscle (rat uterus[27] and rat duodenum[29,30]) methods, illustrated in Figure 2. After the collection of four to six control specimens of perfusate, at five-minute intervals, two intracutaneous injections of histamine were made at a distance of approximately 4 cm. on either side of the collection site. Five-minute samples of the perfusate were collected during 30 to 60 minutes thereafter. Aliquots (0.2 cc.) of the samples were added to the chamber (Fig. 2), and the amplitude of contraction (rat uterus) or relaxation (rat duodenum) induced was expressed as the amount of bradykinin standard required to induce similar contraction or relaxation. Twenty perfusion experiments were performed. Perfusates from the two intact subjects were assayed with the rat uterus method in 10 experiments, with the rat duodenum method in 3 experiments, with the guinea pig ileum method in 2 experiments, and, for protease activity, with a titrimetric method in 2 experiments. In the last method benzoyl arginine ethyl ester (0.01 M) was incubated with perfusate at 37 C in the presence of "tris" buffer (0.25 M, pH 9). Esterase activity was determined by titration of free carboxyl groups formed. Esterase activity determined with this substrate may be used as a measure of protease activity.[31,32] The perfusates from the three patients were assayed with the rat uterus method.

* The perforate needles were especially made by Becton, Dickinson & Co., Rutherford, N. J.

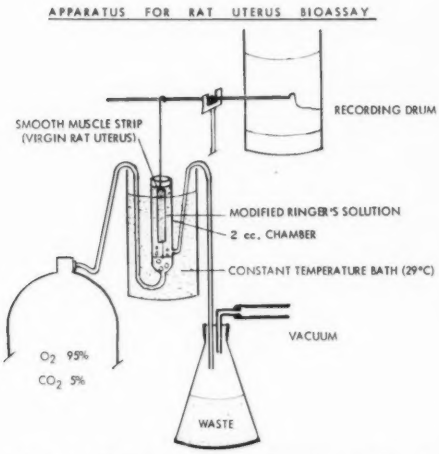

Fig. 2.—The arrangement of apparatus for the method of rat uterus (or rat duodenum) bioassay of perfusate collected according to the method illustrated in Figure 1.

Results:

Control samples of perfusate collected during intervals as long as 60 minutes resulted in contractions equivalent to approximately equal small amounts of bradykinin, after initially higher amounts in the first one or two specimens collected after insertion of the perfusion needles. The presence of this bradykinin-like substance in the control specimens could have resulted in part from trauma secondary to the perfusion procedures and in part from activation of proteolytic enzymes by dilution of serum proteins in the extracellular fluid with saline.

The axon-reflex flares began soon after the skin was injured by the injections of histamine, the flares gradually increasing in area and redness during 15 to 30 minutes. During the first few minutes after the injury, the perfusate contained augmented

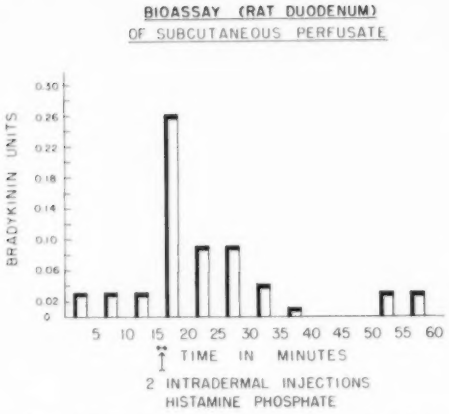

Fig. 3.—Bioassay (rat duodenum) of subcutaneous perfusate collected before and during axon-reflex flare. The axon reflex was induced in two areas by intracutaneous injection of 0.05 cc. of histamine phosphate (1:1,000) at distances of approximately 4 cm. on either side of the perfusion needles (Fig. 1). The duodenum was suspended in de Jalon's solution at 29° C, containing atropine (1×10^{-4} gm/L.), tripelennamine (Pyribenzamine) (1×10^{-4} gm/L.), and BOL (1×10^{-4} gm/L.).

amounts of bradykinin-like substance, as assayed with the rat duodenum (Fig. 3). The fluid collected in the second and third five-minute periods after noxious stimulation also resulted in larger contractions than in the control periods. The flare, however, persisted for a longer period than the increased activity in the perfusate.

The subject with brachial plexus injuries and absence of sensation in the region stimulated and perfused had no flare and no itching following the histamine injection. Also, the perfusate contained no increase in the amount of bradykinin-like material after histamine injection. On the other hand, in the subject who had been deprived of sympathetic innervation only, flare developed after histamine injection, as in the intact subjects, and bradykinin-like polypeptides in the perfusate were increased threefold. This observation will be discussed in more detail later.

Figure 4 shows the results of bioassay of subcutaneous perfusate with the rat uterus. The time course of increased activity differed from that observed with the rat duodenum method. This difference suggests that several substances are present in increased amounts at different times during the axon-reflex flare, since some agents, for example bradykinin, contract the rat uterus but relax the rat duodenum, while others, for example potassium, contract both tissues. Mixtures of such agents may be

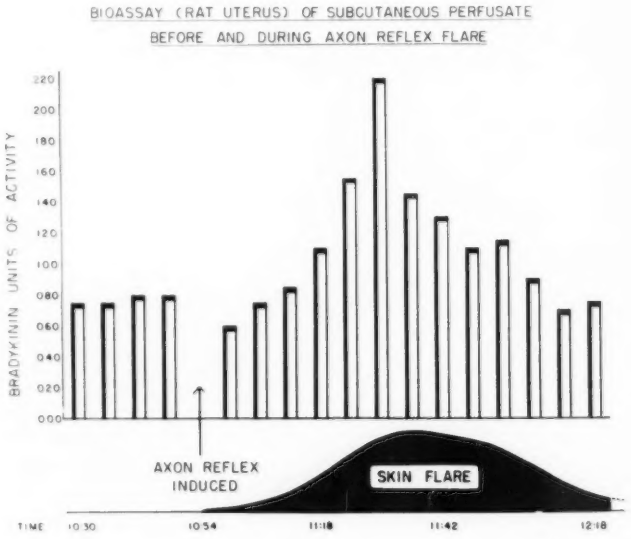

Fig. 4.—Bioassay (rat uterus) of subcutaneous perfusate collected before and during axon-reflex flare. The flare was induced as in Figure 3. The uterus was suspended in de Jalon's solution to which atropine (1×10^{-4} gm/L.), and BOL (1×10^{-4} gm/L.) had been added.

additive in their effects on one preparation but antagonistic on the other.

The forearm of the patient with the "cold allergy" was perfused, as described above. After the collection of several six-minute control specimens of perfusate, an extensive urticarial reaction and flare were induced by the application of cold to the area on either side of the perfusion needles. Bioassay revealed a fivefold increase in bradykinin-like polypeptides.

The properties of the agent responsible for the augmented rat uterus contractions were further defined by study of inhibitors of serotonin and acetylcholine. The rat uterus was suspended in the 2 cc. bath containing de Jalon's solution to which the bromine derivative of lysergic acid diethylamide (1×10^{-4} gm/L.) and atropine (1×10^{-4} gm/L.) had been added. These substances did not inhibit either the contractions induced by control specimens or the increase observed during the axon-reflex flare, indicating that the substance responsible for the increased contractions was not principally serotonin or acetylcholine.

The activity of the perfusate, as defined by its capacity to induce contractions of the rat uterus, was unstable at room temperature. The activity of frozen samples collected in the first five minutes after noxious stimulation increased if the fluid was allowed to stand for three minutes at room temperature but decreased when allowed to stand longer periods; after 10-15 minutes no activity could be demonstrated. The activity of control specimens and that of the specimens gathered subsequent to the first five minutes after noxious stimulation diminished slightly on standing three minutes at room temperature and continued to decrease thereafter. It was postulated that this rapid destruction resulted from peptidase activity in the extracellular fluid. Accordingly, the samples were heated for four minutes in a boiling water bath to destroy such enzymes, and it was found that activity of the perfusate was thus stabilized. Further evidence that the principal agent was a bradykinin-like polypeptide was furnished by the observation that brief (three-minute) incubation with chymotrypsin reduced the activity of the perfusate collected during flare to less than the minimally observable amount that could be detected by the method. This enzyme is known to inactivate polypeptides of the bradykinin-type.[33]

Preliminary studies of the perfusate collected from two subjects indicated the presence of increased amounts of protease, as assayed by the chemical method, using benzoyl arginine ethyl ester as substrate, in the five-minute specimens collected immediately after noxious stimulation, as compared with "control" specimens or the perfusate collected more than five minutes after noxious stimulation. In this laboratory there has been good agreement between protease activity, as determined with this substrate, and "bradykinin-forming" activity, as measured by bioassay with smooth muscle.

Comment:

Since histamine can be released by proteolytic enzymes,[34] and since bradykinin formation is dependent upon such enzymes, it is conceivable that histamine is liberated under conditions associated with the formation of polypeptides. Indeed, other recent experiments in this laboratory indicate that histamine liberation may be a significant factor in the axon and Louvain reflexes.[25] Other agents probably also participate. Serotonin might be released in those reactions in which there is platelet accumulation and breakdown, and possibly escape of serotonin from minute blood vessels into the tissues. Benjamin[35] has recently suggested that noxious stimulation releases intracellular potassium which then activates pain endings. Holton[36] has demonstrated increased adenosinetriphosphate (ATP) content of rabbit ear perfusate following antidromic stimulation. Kunkle[37] has shown that acetylcholine is elevated in cerebrospinal fluid during some vascular headaches of the migraine type. However, since ATP

Properties of a Substance in Subcutaneous Perfusate Present in Increased Amounts During Axon-Reflex Flare

1. Induces itching and dilatation of small vessels and lowers pain thresholds when reinjected intradermally.
2. Increases vessel permeability (outflow volume of perfusate increases two- to threefold during flare).
3. Contracts isolated rat uterus and guinea pig ileum and relaxes isolated rat duodenum.
4. Enhanced smooth muscle contractions are not inhibited by antihistamines, the bromine derivative of lysergic acid diethylamide (BOL), or atropine in amounts that inhibit histamine, serotonin, and acetylcholine, respectively. Thus, none of these is the principal active agent, although they or others may also participate.
5. Rapidly loses its capacity to induce contractions of smooth muscle on standing at room temperature (in 10 to 20 minutes).
6. Its activity is stabilized by four minutes of heating in a boiling water bath.
7. The activity of the heat-stabilized substance is destroyed after brief (15-minutes) incubation with chymotrypsin; i.e., the active agent is a peptide.

and acetylcholine are usually rapidly destroyed in tissue, their significance in sustained inflammatory reactions is difficult to evaluate.

It has been shown that when mixtures containing bradykinin prepared by incubation of trypsin with pseudoglobulin were injected into the skin, they induced burning pain and itching sensations.[38-40] The accompanying Table lists these and other properties of the perfusate supporting the view that the principal active agent liberated into the perfusate is a bradykinin-type polypeptide.

At least three possibilities concerning the origin of protease and polypeptides are compatible with the data here presented. The first is based on the fact that blood itself contains an enzyme (plasmin) that can form bradykinin-like polypeptides.[41] According to the views of Lewis,[42] the entrance of this enzyme system into the interstitial spaces as a consequence of vasodilatation induced by some unknown mechanism could result secondarily in the formation of vasodilator polypeptides (plasma kinins).

The second possibility is that neurogenic influences release metabolites that convert plasminogen already present in extracellular fluid to the active proteolytic enzyme, plasmin, which then results in polypeptide formation.

A third, and to us attractive, possibility is that a neurogenic humoral agent, such as acetylcholine, alters membrane permeability of many varieties of cells to release intracellular proteolytic enzyme, which then acts on protein in extracellular fluid to produce polypeptides of the bradykinin type, as well as other potent agents, such as histamine and serotonin.

Hilton and Lewis,[43] analyzing venous perfusate from the skin of the cat, failed to observe bradykinin activity following antidromic stimulation of the saphenous nerve. However, the degree of vasodilatation in these circumstances was slight, and an associated small increase in bradykinin might conceivably have been beyond the limitations of the method to detect.

Protease activity has long been held to be relevant to inflammation,[44] and Ungar[45] recently has traced the evolution of the concept that proteolytic-enzyme activation is a primary feature of the antigen-antibody reaction. Also, Beraldo, in 1950,[46] demonstrated that bradykinin is formed during anaphylactic shock. Thus, on the basis of these latter studies and those reported in the present communication, it appears that bradykinin formation is a common biochemical link between nervous system activity and the antigen-antibody reaction.

II. Demonstration That the Inflammatory Response Can Be Modified by Neural Activity Integrated at the Brain Stem and Hypothalamic Levels: Thermoregulatory Reflexes

A. Thermoregulatory reflex vasodilatation is accompanied by lowered pain threshold.

The vasomotor reactions in the skin as part of the body's thermoregulatory devices can be dramatically demonstrated by the study of the nonimmersed surface of a subject partially immersed in hot water. Under these circumstances the skin of the nonimmersed portion becomes flushed, the temperature elevated, and sweating aug-

mented. Graham et al.[47] showed that during the initial flush there was a transient lowering of the pain threshold in the skin, as measured by the thermal radiation technique. Bilisoly et al.[26] also induced reflex vasodilatation in the skin of the arms by immersing the subject's feet and legs in hot water. By using the point at which pulling a hair first caused pain as a pain-threshold measurement, they demonstrated a transient lowered pain threshold during the initial flush. This lowered threshold was not dependent upon an elevated skin temperature per se.

B. Thermoregulatory reflexes can modify the vaosdilatation accompanying the axon reflex.

Two experiments were performed in order to ascertain whether the magnitude of the flare of the axon reflex could be modified by superimposing the effects of the thermoregulatory reflexes just described. Two of us served as subjects. First, the unclothed subject was chilled in moving air at a room temperature of approximately 14 C. After 30 minutes of chilling, the skin of one forearm was injured by intracutaneous injection of histamine phosphate (0.05 cc. of 1:1,000 solution). The extent of axon-reflex flare was outlined in ink and a tracing made on thin paper for comparison with the flares (*a*) resulting from a similar injury an hour later, when the subject was again comfortably warm, and with the flares (*b*) induced after the subject had been heated by immersion of the feet and legs in hot water. The flares induced when the subject was chilled were invariably far smaller in area than those in control conditions or during heating (Fig. 5).

C. The magnitude of inflammatory reaction and tissue damage in response to noxious stimulation is enhanced during thermoregulatory reflex vasodilatation.

In the second series, of five experiments on three healthy subjects, the skin of the forearms was injured by a standard thermal stimulus (500/mc/sec/sq. cm. for three seconds) applied to one arm before the subject was immersed (control, "comfortably warm" conditions) and to the other arm when the subject was being heated by immersion of the feet and legs in hot (42 C) water and just as the skin temperature of the forearm was beginning to rise. If the skin temperature had become elevated, the skin was gently cooled locally with a forced draft of air to the temperature of the control arm at the time it had been injured. Skin temperatures were recorded by a multichannel continuous recorder. The

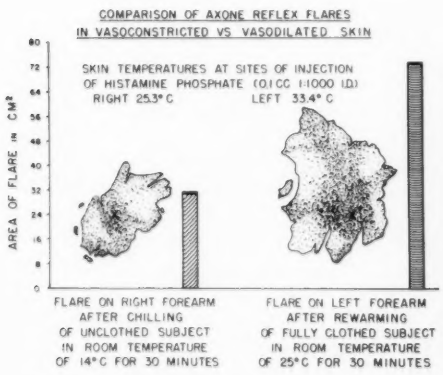

Fig. 5.—Comparison of axon-reflex flares in the chilled vs. the normal, warm subject.

Fig. 6.—Photographs of the results of burns resulting from application of similar noxious stimulation (500/mc/sq. cm/sec. for three seconds) to the right arm just before, and to the left arm during, immersion of the feet and legs in hot water. The burns on the left arm were made in the initial phase of vasodilatation and can be seen to be more extensive than on the right, control arm.

magnitude of the inflammatory reaction was estimated and photographed each day during the next 12 days. In all three subjects, and in all experiments, the injuries sustained on the arms noxiously stimulated during immersion of the feet and legs were significantly greater than those on the control arms; an example is illustrated in Figure 6. This picture was taken three days after the skin had been burned. The skin temperature just before the skin was burned was 34.0 C (93.2 F) on the right control arm and 33.7 C (92.6 F) on the left, cooled, though actively vasodilating, arm.

Comment:

The experiments with chilling the body at low room temperature, and with raising body temperature by immersion in hot water, implicating the thermoregulatory centers, demonstrate that activity within the central nervous system integrated at the brain stem and hypothalamic levels can modify the effects of the axon reflex and the inflammatory reaction to noxious stimulation. Fox and Hilton [28] demonstrated that the flush induced on the forearm by immersing the rest of the body in hot water is accompanied by an increase of bradykinin-like material in the perfused subcutaneous spaces. It may thus be inferred that central neural activity can lead to increased amounts of proteolytic enzymes and bradykinin-like polypeptides in the peripheral tissues in which there is thermoregulatory reflex vasodilatation.

D. Activation of sweat glands is not essential to bradykinin formation during neurogenic vasodilatation in the skin.

Fox and Hilton [28] inferred that heightened sweat-gland activity is responsible for the release of bradykinin-forming enzymes during vasodilatation induced by indirect heating. Experiments were undertaken to clarify whether or not sweat-gland activation is indeed essential to the increased production of bradykinin-like polypeptides during axon reflex, by study of a subject deprived of sympathetic innervation in the region examined. The patient, one with Raynaud's syndrome, 12 years earlier had undergone bilateral upper thoracic sympathectomy and bilateral anterior rhizotomy of the first thoracic nerve. The sympathetic chain was divided below the third ganglion, and the second and third intercostal nerves were resected. The stellate, second, and third ganglia and the central attachment of the first thoracic root were left intact. Also, the first thoracic anterior root was divided bilaterally, leaving the posterior roots intact.

The left forearm was perfused as described above (Fig. 1). Histamine phosphate (0.05 cc. of 1:1,000 solution) was injected intradermally approximately 4 cm. on either side of the perfusion site to injure the skin and induce an axon reflex. A "flare" developed that was similar to that observed in intact subjects. However, there was no change in the electrical resistance of the implicated skin and no evidence of sweating with the starch-iodine method. Nevertheless, a threefold increase in bradykinin-like substance was found in the perfusate collected during the flares.

Comment:

These observations argue against the suggestion of Fox and Hilton [28] that activation of sweat glands is a required step in the release of bradykinin-forming enzyme during neurogenic vasodilatation and heightened metabolism in the subcutaneous skin and tissues, but do not deny that the sweat glands when secreting may contribute to formation of bradykinin-like substance. Indeed, there is nothing to indicate that the release of intracellular protease during heightened cellular activity is limited to specific cells. Chapman and Wolff [48] demonstrated increased amounts of kinin-forming enzymes in cerebrospinal fluid following noxious stimulation. Ansell and Richter [49] demonstrated a neutral proteinase in whole-brain slices, and Ungar [50] showed that protease activity of whole-brain slices is increased following stimulation of sciatic nerve.

III. Demonstration That Central Nervous System Activity Integrated at the Highest Level Modifies the Inflammatory Reaction in the Periphery

A. Spontaneous urticaria may occur in situations perceived as threatening.

Graham, studying patients with urticaria about 10 years ago,[51] showed in situations perceived as threatening, or during the discussion of them, that the tone of the minute vessels in the skin was reduced and permeability increased. Under these circumstances heretofore non-noxious stimuli, both mechanical and chemical, became capable of inducing flush, itching, and urticaria, and in some instances these latter phenomena occurred spontaneously.

Although careful descriptions of methods and results are rare, it has long been alleged that lesions in the skin can be induced by suggestion during hypnosis. A recent and better-documented instance is that of Ullman, who induced erythema with blister formation that was noted at the end of an hour, and was fully developed approximately four hours later.[52]

In this laboratory it was possible during hypnosis to demonstrate the occurrence of erythema and whealing in response to the repeated application of a metal rod at room temperature to the skin of the forearm, accompanied by the suggestion that the rod was hot and would burn the skin.

B. Suggestion during hypnosis may modify the magnitude of vascular response and the degree of tissue damage in the skin following noxious stimulation.

The above observation that erythema could be induced by suggestion was further evidence that activities of the highest integrative levels of the nervous system could modify the magnitude of inflammatory reactions in the periphery. Therefore, experiments were designed to demonstrate that the degree of inflammatory response and tissue damage to a standard noxious stimulation could be augmented or diminished by activity of the central nervous system integrated at the highest levels. As an aid in manipulating these activities by the suggestion of relevant symbols, the hypnotic state was induced. It was, however, recognized that the hypnotic state per se is not essential to the effects associated with suggestion, symbols, and memories.

Method:

Thirteen adult men and women served as subjects. Three of these were patients who had spontaneously occurring urticaria. The remainder were healthy and free of skin disorders.

Experiments were conducted in a quiet, semi-darkened, comfortably cool room. Thermocouples were attached to the subject's arms and a series of control temperatures recorded by means of a multichannel recording instrument. Finger cuffs for recording of the plethysmograms were attached to the middle finger of each hand and control recordings made.

The subject was hypnotized in the conventional manner. As soon as a state of moderate to deep hypnosis had been established, it was suggested either that one arm was "normal" or that it was "numb," "wooden," and devoid of sensation ("anesthetic"). It was then suggested that the other arm was painful, burning, damaged, and exceedingly sensitive, i.e., "vulnerable." Furthermore, it was suggested that severe injury to this "vulnerable" arm, which would cause even greater pain and damage, was about to occur. The "vulnerable" arm was then exposed on three spots, blackened with India ink, to standard noxious stimulation (500/mc/sq. cm/sec. for three seconds). After an interval of 15 to 30 minutes, during which hypnosis was continued, suggestions that the other arm was either "anesthetic" or "normal" were repeated and reinforced. It was then similarly exposed on three spots to the standard noxious stimulation. In some experiments the order of exposing the "vulnerable" and "anesthetic" arm to noxious stimulation was reversed. Also, the right arm was suggested to be "vulnerable" in some experiments, the left in others. In some experiments the suggestions of "vulnerability" for one arm and "anesthesia" for the other were made simultaneously, and the noxious stimulation was applied during the same interval alternately on the two arms.

The inflammatory reaction and tissue damage were assessed by observations and measurements of area, intensity, and duration of erythema, edema, blister formation, necrosis, and, when present, residual scar formation. Colored photographs were made approximately 20 minutes after the end of an experiment and at 24-hour intervals for about 2 weeks.

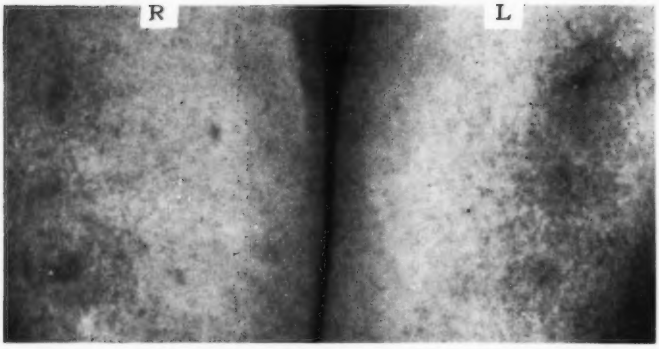

Fig. 7.—Photograph of the arms of Subject A. made approximately half an hour after noxious thermal stimulation during hypnosis. The right arm as suggested to be "vulnerable," the left arm "anesthetic." The burns were made in quick alternation from one arm to the other within a period of 30 seconds. Note the more extensive erythematous reaction surrounding the burns on the "vulnerable" (right) arm.

In one subject the subcutaneous spaces in the zones of axon-reflex flares induced by the noxious stimulation were perfused. The method of perfusing the subcutaneous space is a modification of that of Fox and Hilton.[28] Figure 12 shows the method of inflow and outflow, using perforate needles.

Results:

The 13 subjects were hypnotized in 40 experiments. During 12 of these experiments increased pain and damage were suggested in one arm, and suggestions that the arm on the opposite side was normally sensitive were made. The inflammatory reaction and tissue damage were greater on the side of suggested "vulnerability" in 9 of this series of 12 experiments; in 1 experiment increased damage was observed on the side of suggested normal sensitivity, and in 2 experiments no difference was noted. In 27 experiments it was suggested that one arm was "vulnerable" and that the other arm was "anesthetic." In one experiment greater damage occurred in the arm of suggested "anesthesia." In six experiments no difference was observed in the two arms. However, in 20 of this series of 27 experiments the inflammatory reaction was greater on the side of suggested pain and damage. In one experiment it was suggested that one arm was anesthetic, the other normally sensitive. The reaction was far greater on the normal side. Although the contrast was greatest in the magnitude of reaction between suggested "anesthesia" and suggested "vulnerability," it was also evident that the effect of suggested "anesthesia" was to suppress the inflammatory reaction, as contrasted with the effect of suggestion of normality. In Figures 7, 8, 9, and 10 are

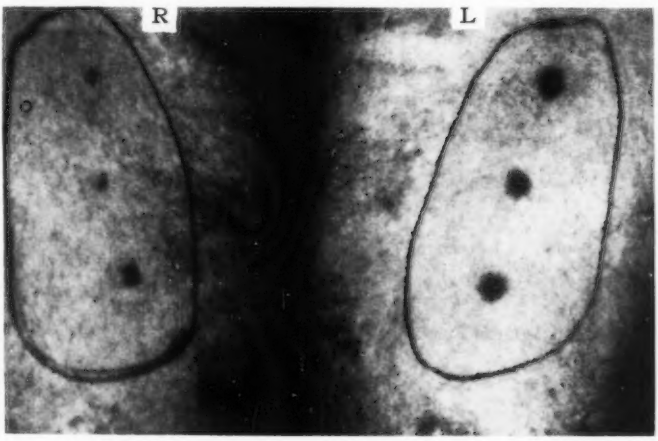

Fig. 8.—The arms of Subject A. photographed four days later than the photographs of Figure 7. Note the greater tissue damage on the "vulnerable," right arm, as compared with that on the "anesthetic," left arm, resulting from identical intensities and durations of noxious thermal stimulation.

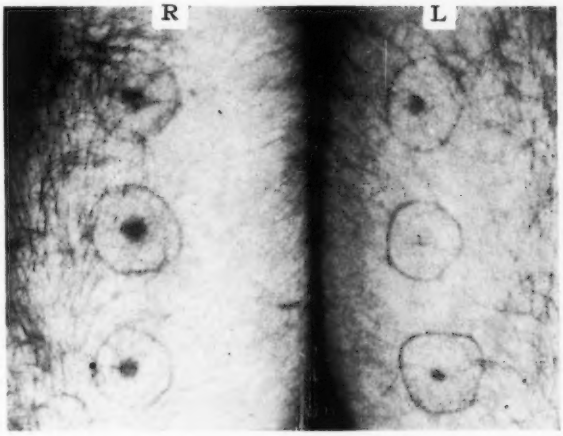

Fig. 9.—Photograph of the arms of Subject B., made three days after noxious thermal stimulation during hypnosis. The burns were made in quick alternation from one arm to the other while the left arm was being suggested as "vulnerable" and the right arm as "anesthetic." Note the greater tissue damage on the "vulnerable," left arm, as compared with that on the "anesthetic," right arm, resulting from identical intensities and duration of noxious thermal stimulation.

shown the greater damage in the vulnerable arms and the less severe damage in the "anesthetic" arms after identical thermal stimulation of the two limbs. One patient who complained of spontaneously occurring urticaria developed urticarial reactions in other parts of her "vulnerable" arm following noxious stimulation by heat (500/mc/sq. cm/sec. for three seconds). Urticaria was not observed on the "anesthetic" arm at this time.

In two experiments in two subjects, two exposures of 500 mc. and two exposures of 410 mc. were made on each arm. The less intense stimulation was used in order to ascertain whether the effects of highest level functions would be more conspicuous when the damaging stimulus was less intense. It was shown that when anesthesia was suggested in the one subject no visible damage could be perceived 18 hours after the stimulation with 410 mc., whereas when

Fig. 10.—Photograph of the arms of Subject C. four days after noxious thermal stimulation during hypnosis. While the right arm was suggested to be "anesthetic," three thermal burns were made. Hypnosis was continued, and half an hour later suggestions of "vulnerability," i.e., that the left arm had already been damaged and was painful and sensitive, were made; and it was repeated several times that it would be burned and damaged again. During these suggestions noxious thermal stimulation was applied three times. Note the greater burns on the left, the "vulnerable," arm.

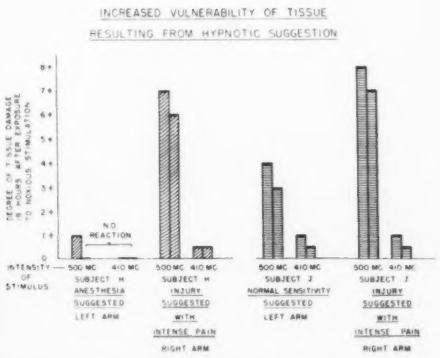

Fig. 11.—Diagrammatic representation of increased vulnerability of tissue induced during hypnotic suggestion in two subjects, H and J. Two intensities of thermal stimulation were used, and the effects of suggested anesthesia compared with those of "vulnerability" in Subject H, and the effects of suggested normal sensitivity compared with those of "vulnerability" in Subject J.

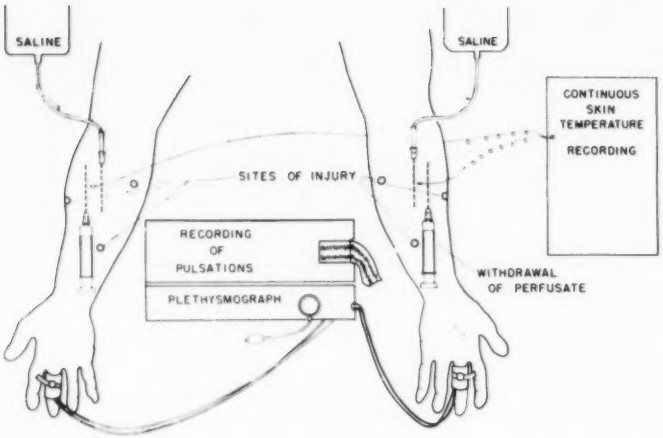

Fig. 12.—Arrangement of apparatus and recording devices for perfusion of two arms, collection of perfusate, recording of finger pulsations, and measurement and recording of skin temperature, with the sites of injury indicated. Four No. 20, 2-in.-long, perforate needles were inserted into the subcutaneous spaces. Thermocouples for skin-temperature measurement were attached to the skin at a distance of 2 cm. from the site of injury.

injury with intense pain was suggested, this less intense stimulus produced readily detectable lesions.

In the second subject the difference in reaction between the arm with normal sensitivity and the one with suggested injury and intense pain was less striking, but the inflammatory response to the more intense stimulation was conspicuous (Fig. 11) on the side of suggested "vulnerability."

Experiments were then designed to ascertain the nature of the relevant tissue responses that could explain the greater amount of damage in the "vulnerable" arms. Figure 12 shows the two arms prepared for skin temperature, for finger plethysmographic recordings, and for the collection of perfusate. These observations were made before and during the period of hypnosis, both before and after the application of noxious stimuli. In this series no significant differences in the amplitude of finger pulsations, in the skin temperature of the arms, or in the bradykinin content of the perfusates could be observed between the "anesthetic" and the "vulnerable" arm before the damaging stimulus was applied, although other experiments in this laboratory indicate that such differences may be induced during suggestion alone. Under the given experimental circumstances reported here, in response to noxious stimulation there was a greater and longer-sustained rise in the amplitude of the finger pulsations and in the skin temperature of the "vulnerable" arm (Figs. 13 and 14), as well as a greater increase of bradykinin content

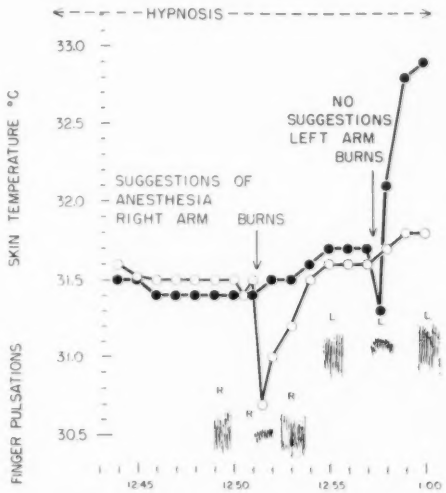

Fig. 13.—Measurements during hypnosis of the skin temperature and amplitude of finger pulsations of the right, "anesthetic" arm and of the left arm, suggested to be normally sensitive. Note the larger initial vasoconstriction, as indicated by fall in skin temperature in the arm suggested to be anesthetic (right) and the markedly reduced subsequent vasodilatation as compared with the reaction to the burns on the normally sensitive (left) side. The absence of, or the minimal, vasodilatation after injury in the arm suggested to be "anesthetic" affords a partial explanation of the minimal injury after noxious stimulation.

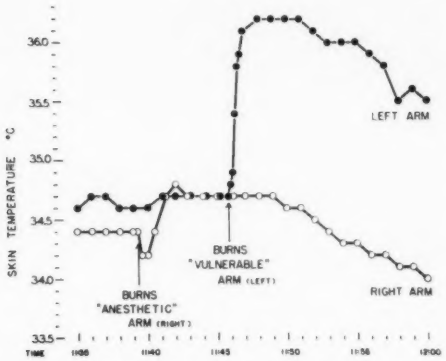

Fig. 14. Measurements during hypnosis of the skin temperatures of the right ("anesthetic") arm and the left ("vulnerable") arm. Previous to and during the application of burns (500 mc/sq. cm/sec. for three seconds) the right arm was suggested to be numb, anesthetic, and without feeling, whereas the left arm was suggested to have been damaged, to be very painful, and about to be even more painfully burned. Note the predictably greater degree and more persistent rise of skin temperature after suggestion of damage, indicating the pertinence of vasodilatation to the enhanced inflammatory reaction to noxious stimulation.

of the perfusate from this arm (Fig. 15), as compared with the "anesthetic" arm. The greater rise in skin temperature occurred in all experiments in which damage was greater on the "vulnerable" arm. A corresponding increase in finger pulsations was less predictable.

Comment:

Both the experiments with immersion in hot water, implicating the thermoregulatory centers in the brain stem and hypothalamus, and the experiments with hypnosis, implicating the highest levels of neural integration, demonstrate that activity within the central nervous system at several levels can augment the effects of the axon reflex. The occurrence of spontaneous urticaria observed in one susceptible subject suggests a widespread heightened reactivity in the vulnerable arm during the threatening situation created by suggestion and by burns.

It thus appears that the subject's perceptions and attitudes may be relevant to neural activities that engender or enhance inflammatory reactions. The liberation or accumulation of proteolytic enzymes in the periphery and the subsequent formation of a bradykinin-like humoral agent are implicated in this reaction.

Enhanced inflammation has been shown to be effective in combating invasion by microorganisms and in the rapid elimination of

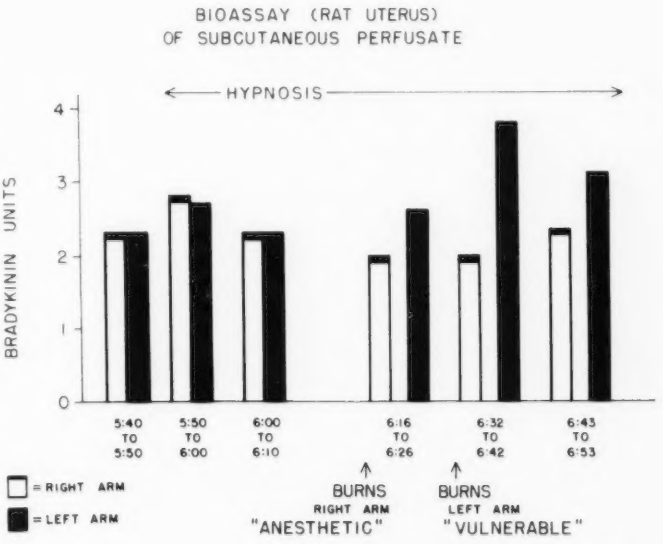

Fig. 15. — Bioassay of the subcutaneous perfusate, expressed as units of a standard preparation of bradykinin inducing equivalent contractions of the rat uterus. After injury of the "vulnerable" arm during hypnosis there was more "bradykinin" activity in the perfusate from the flare zones induced by the thermal injury than in the perfusate from the arm suggested to be "anesthetic." Decimal points should precede numbers on left side.

tissue-breakdown products of injury. The view is proposed that man includes among his adaptive and protective devices neural reactions integrated at the highest levels that heighten inflammation in the peripheral tissues and increase the local susceptibility to injury, thus enhancing the protection of the whole organism at the cost of the integrity of a part. Such reaction at times may be essential to survival, but, if evoked inappropriately or excessively, may contribute to disease, since non-noxious stimulation becomes noxious and mildly damaging stimuli result in greater injury.

Summary and Conclusion

In the flare zone of the axon reflex during the initial phase of the period of vasodilatation, pain threshold was lowered, and tissue damage and the inflammatory response to noxious stimulation were enhanced. At this time there was liberated or accumulated in the skin and subsurface tissue fluids a pharmacodynamically active substance. This substance induced itching, local vasodilatation, and edema, lowered blood pressure, lowered the pain threshold, induced delayed and slow contraction of the rat uterus and guinea pig ileum, and induced relaxation of the rat duodenum. It deteriorated at room temperatures, was stabilized by boiling, and was destroyed by chymotrypsin. It was not acetylcholine, histamine, or serotonin, although these and other relevant agents may also have been present. It had many of the properties of a polypeptide of the bradykinin type.

During the initial phase of thermoregulatory-reflex vasodilatation in the arm stemming from immersion of the feet and legs in hot water, the pain threshold was lowered, and tissue damage and the inflammatory response to noxious stimulation were enhanced.

After standard amounts of noxious stimulation on the forearm during hypnosis, decreased inflammatory reaction and tissue damage were observed when the suggestion was made that the arm was insensitive and numb and would not be hurt, "anesthetic," as compared with the reaction and tissue damage of the other arm, which was suggested to be normally sensitive.

After standard amounts of noxious stimulation on the forearm during hypnosis, increased inflammatory reaction and tissue damage were observed in subjects who had received the suggestion that the forearm was tender, painful, and injured, "vulnerable," as compared with arms suggested to be normally sensitive or "anesthetic." Recordings of finger-pulse amplitude and skin temperature indicated that local vasodilatation following exposure to noxious stimulation was larger in magnitude, and persisted longer, in the "vulnerable" arm. The subcutaneous perfusate from the arm suggested to be painful, tender, and damaged developed a greater increase of bradykinin-like substance in response to standard noxious stimulation than did that from the arm suggested to be "anesthetic."

Neural activity involving the segmental or axon levels, the brain stem, and hypothalamic levels, as well as the subcortical and cortical levels, can alter the reactions in the peripheral tissues subserved in such a way as to augment inflammation and increase local tissue damage in reaction to noxious stimulation. Proteolytic enzymes and a bradykinin-like polypeptide are implicated in these enhanced reactions.

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News and Comment

ANNOUNCEMENTS

"Medical Department, United States Army."—The Historical Unit of the U.S. Army Medical Service is writing and publishing the series of volumes entitled "Medical Department, United States Army," which relate the history of World War II. The authors and editors of these books are among the outstanding medical and medicomilitary authorities in the United States

The Surgeon General of the Army is particularly anxious that information of the existence and availability of these volumes be circulated as widely as possible among members of the profession. The medical history of World War I did not fulfill its potential usefulness because so few medical personnel knew about it and had to learn, the hard way, the lessons spelled out in it. It is hoped that this will not recur in the unhappy event of another war.

To date, 14 volumes have been published in a proposed series of 55. All of these books are available from the Superintendent of Documents, Government Printing Office, Washington 25, D.C.

Council on Medical Television.—The Council on Medical Television will hold its first meeting Oct. 15-16, 1959, at the Clinical Center, National Institutes of Health, Bethesda, Md. The Council, which consists of representatives of the various types of organizations and institutions concerned with using television as a tool for undergraduate and postgraduate medical education, was recently established under the auspices of the Institute for Advancement of Medical Communication to serve as an advisory and planning group in meeting the challenges and realizing the potential of this new medium for communication. Organizations interested in sending observers to this meeting may contact the Institute for Advancement of Medical Communication, 33 E. 68th St., New York 21.

PERSONAL

Appointment of Dr. Joseph L. Camp.—The appointment of Dr. Joseph L. Camp as deputy assistant commissioner in the Department of Mental Hygiene was announced today by Dr. Paul H. Hoch, Commissioner of Mental Hygiene.

Dr. Camp, assistant director at Letchworth Village, Thiells, N.Y., will assume his new post on Aug. 13. His duties will include medical inspection functions particularly in the mid-Hudson area. He will also assist in the administration of the Department's program for the retarded and with administrative responsibilities relating to staff functions of the Department. The salary for the appointment is $12,998 to $15,188.

SOCIETY NEWS

American Electroencephalographic Society.—The following officers were elected at the June, 1959, meeting of the American Electroencephalographic Society in Atlantic City.

President:	Dr. Arthur A. Ward Jr. Division of Neurosurgery University of Washington Medical School Seattle 5
President-Elect:	Dr. Jerome K. Merlis EEG Laboratory University Hospital Baltimore 1
Secretary:	Dr. George A. Ulett, Malcolm Bliss Mental Health Center 1420 Grattan St. St. Louis
Treasurer:	Dr. Isadore S. Zfass 2502 Monument Ave. Richmond 20, Va.

GENERAL

The Training School at Vineland, N.J.—The Training School would like to offer for one-time showing to groups or classes interested in mental retardation a 28-minute sound-on-film production entitled "Into the Sunlight." The film, produced in cooperation with NBC and narrated by Don Goddard of ABC-TV, is in block and white, and there is no charge except for return mailing and insurance of $100.

Write to Public Relations Department, The Training School, Vineland, N.J.

Books

Mirage of Health. By Rene Dubos. Volume 22 of World Perspective Series. Edited by Ruth Nanda Anshen. Price, $4. Pp. 236. Harper & Brothers, 49 E. 33d St., New York 16, 1959.

The publishers and chief editor, Dr. Ruth Nanda Anshen, with a distinguished board of editors, have added to their series of monographs, known as the "World Perspectives Series," one of the most important essays in our time—Rene Dubos' "Mirage of Health." This, coming after Edmund W. Sinnott's able contribution, "Matter, Mind and Man," makes this series of little books one of the memorable efforts of this century. All authors of the series are outstanding senior scholars who take the opportunity offered to construct general theory and formulation. The essays are well written and state simply those inferences, reflections, and prospects that came after a life of close application by thoughtful persons in any discipline.

Rene Dubos' monograph is outstandingly good. It is written freshly, lightly, elegantly, and with humor; it should have a major impact on contemporary thought. The concepts, figures, and utterances are truly those of a biologist, one long accustomed to view living phenomena and interpret what he sees in terms of living stuff, instead of in terms of inept physical or mechanical models. He gives to the experiments of nature their proper place alongside the more modest, designed experiments of the laboratory. He embraces exact methods and formulae of physics and chemistry and sees biostatistical methods as useful supplementary tools, but always as a biologist. He recognizes the limitations of his methods—especially the fact that he introduces limitations of his own choice—also the countless variables and difficulties of prediction.

The essence of his essay is that living creatures, given time, will work out some sort of living arrangement with one another. During the process of achieving ecological balance, damage and death come to many creatures; and if the process is too rapid, this destructive effect is augmented. The relationship of different living forms is less that of survival of the fittest and more that of a dovetailing, as all participants make some sort of compromise and rearrangement within, and sometimes around, themselves. Those who cannot change, or change too slowly, cannot attain this ecological balance and go under; but most species go on, and for the most part with only inconspicuous outward modifications in individual structure.

Dubos has much to say about man but starts with micro-organisms, whose habits and peculiarities he knows as do few others. He finds they cannot easily be classified as pathogens for man, and sees that only when the soil is right in man do they succeed in injuring him. Indeed, any organism, he holds, may become pathogenic under certain circumstances within the host.

Causation in disease, particularly as regards infections, he sees as an almost unmanageable concept, since any of myriad factors in the steps by which a creature becomes sick may be looked upon as "etiological."

He even goes so far to say that a man's philosophy, and the economic and social changes that he may be exposed to, are probably more important to his chances of becoming sick than are any specific micro-organisms. All factors that alter well-established and stable relationships among living creatures may be initiators of disease, and the more violent and rapid these changes (especially when through age, phase, or season some major internal rearrangements are being made) the more hazardous are the effects of alterations in the relationship between host and invader. Disruption of an ecological balance by ostensibly benign interlopers on land, sea, or within the body of man may be the firing charge that explodes catastrophically in an individual, or in a continent, as during the great plagues.

Inversely, living forms with remarkably different goals can establish ecological balance among themselves, given sufficient time and the continued stabilization of other factors in their relation to each other. But, he properly warns, "symbiosis is usually on the threshold of disease." Referring to contemporary human problems, he says: "Man can eventually become adapted to almost anything, but adaptation demands more time than is allowed by the increased tempo at which changes are presently taking place."

He has little sympathy with the complicated verbal concepts that comfort, but inhibit thought. "The concrete facts of microbiological science have been on the whole easy to discover and their understanding presents no abstruse problems. The real difficulty has been rather to explain why so many varieties of microorganisms, endowed with the ability to kill, usually produce only self-limiting disease processes and often cause no discernible harm even though they persist in the body. True to Goethe's remark that where understanding fails there immediately comes a word to take its place, many words have been used to deal with this apparent anomaly. Abstract concepts, such as resistance or susceptibility of the host, virulence, attenuation, invasiveness, and toxicity of the parasite have all been invoked as if they corresponded to real entities, and could be incorporated into a formula to account for the outcome of infectious processes. Unfortunately these words refer not to characteristics inherent in the host or the parasites, but merely to states of relationship between the two. And these relationships are governed by biological properties that still transcend description in the conventional terms of present day physical chemical sciences."

Important for our time is the realization that great therapeutic triumphs have often occurred when, for whatever reason, infectious agents have lost their vigor. After citing the remarkable rise and fall of such vicious killers as measles, smallpox, tuberculosis, cholera, and plague, and indicating that "miracle" drugs, despite man's self-adulation, have had but a modest role in their defeat, he points out wryly that anyone who energetically scoops pails of water from the waves during a falling tide may have the delusion that he is bailing out the ocean.

Dubos is truly a holist. The mind-body dichotomy holds no attraction for him, since he sees the human spirit as the product of the whole man and his past and holds with Tennyson that "I am a part of all that I have met."

Having made major contributions to medicine and the elimination of disease, Dubos concludes that medicine is an art and must remain so, since the proper evaluation of a host of factors not reducible to formulae must be taken into account in any given patient, since the latter's goals and purposes must remain individual, as must each person's past.

Thus, in coming to the nature of man, he accepts aspiration, creativity, abhorrence of boredom, and need of change as central aspects of human activity. He sees him always during his greatest vigor ready to risk the safe, the certain, the predictable, and the secure position for one of exploration, adventure, uncertainty, and challenge. In so doing, man seriously jeopardizes the ecological balance most compatible with health and so must, to be a man, run the risk of sickness and death. This is man's fate and the price he must pay for his nature. Hence the utopias, the idyllic pastoral tranquility he dreams and talks about, he forgoes to fulfill his human mission.

This concept of disease, pain, suffering, and death as sequelae of risks involved in being man has an ancient classical ring and, despite much to the contrary in the modern mood, is amply supported by other studies that show sickness to be but an aspect of a way of life, and the most well not necessarily the best humans.

The book is replete with evidence for these basic views. Whereas he touches lightly on the hazardous aspect of a most important feature of human ecology, namely, the intimate relations of one person with another and the implications of disrupted relationships of the intimate kind (child-parent, man and wife, brother *vs.* brother, employer-employee) as regards the occurrence of disease, he always implies that man's goals, values, frustrations, conflicts, and deprivations of love and approval are essential to an understanding of human health and disease.

It is perhaps at this juncture that the argument becomes of special interest to those concerned with the nervous system and problems of adaptation. Dubos cites countless examples of the flexibility of lower forms and indicates how, without complicated neural equipment, organisms weather many storms of change and stress. What, then, does man bring to the scene with his elaborate capacity to respond to symbols and to extrapolate from experience? Certainly, his triumphs over other animal forms in a few instances are striking, but doubtful in others, notably over certain insects and micro-organisms. He often immoderately attributes such victories to his rational processes and "taking steps," when, indeed, far more primitive biological devices in both himself and his opponents have been silently at work. But oustanding is his capacity for interaction with his environment in which communication between men is striking; his ability to shape to a modest extent his immediate world, to plan and to hope.

Growing out of a different body of experience are the similar concepts of this reviewer: that the mind or spirit of man is confined to no one part, that the human brain is a mighty contributor and a device for the definition and achievement of goals. But man's brain demands a ransom, namely, that he be in an environment that allows of interaction, since otherwise the brain fails. Without suitable challenge, stimulation, and provocation he becomes inert, listless, and demoralized. The cost is his knowledge of the inevitability of his fate, his collapse when interaction is blocked and communication fails, and his need to run risks, accept challenges, precipitate events, and induce rapid change. Thus, to keep his special equipment in good running order, he must jeopardize survival.

This remarkable essay is essential reading matter for anyone interested in man, and especially for those who are trying to deal with him when he is sick.

HAROLD G. WOLFF, M.D.

Pathology of Tumours of the Nervous System. By Dorothy S. Russell and L. J. Rubinstein. Price, $13.50. Pp. 318. Edward Arnold & Co., 41-43 Maddox St., London, W. 1 (Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore, exclusive American agents), 1959.

This is a companion volume to Greenfield's "Neuropathology," and it was originally planned that he should edit it. Although it is regrettable that he was unable, because of illness, to do so, it is doubtful that he could have produced a better book. In addition to true neoplasms, tumor-like abnormalities are included, but not granulomas or parasites, which were adequately presented in Greenfield's volume.

In the discussion of pathogenesis, the authors admit that a slight blow on the head can "unmask a glioma already present" but go on to remark that the problem of the relation of trauma to tumor growth is "more difficult when a period of months or even years has elapsed." "The sequence of events may be suggestive. . . . On the other hand when the vast legacy of war and civic brain injuries, unaccompanied by neoplastic disease, is weighed in the balance it must be concluded that these few cases are more curious than significant."

The discussion of congenital tumors of maldevelopmental origin follows accepted lines. Various types of meningiomas are described, since the pathologist is "required to be familiar with the rather wide spectrum presented by meningiomas as a whole." The microglial cells of the central nervous system surely do not fulfill the definition given of the reticular tissue. They are not "fixed cells supported by a framework of fibrils," nor is it proved that they "evolve from the primitive reticulum cells"; but tumors supposed to derive from them might as well be described in this heterogeneous group of Chapter 4 as elsewhere. The classification of the tumors and hamartomas of blood vessels "differs from that of Cushing and Bailey only in the addition of a separate group, the cavernous angiomas, to the class of vascular malformations."

In their discussion of tumors of neuroepithelial origin, all of the types described in the original monograph of Bailey and Cushing are recognized, and necessarily so, since they can be identified in any extensive collection of these tumors, however it be subdivided. The necessity for describing these types is the same as that given by the authors for describing the various types of meningiomas—the pathologist "is required to be familiar with the rather wide spectrum." This is also the reason for rejecting the excessively simplified scheme of Kernohan, dictated in the first place by the demands of surgeons who were interested only in having an estimate of the malignancy of the tumors they uncovered at the operating table as a guide to operative procedure. The literature concerning these neuroepithelial tumors is adequately covered, and the varying theories of their origins are described.

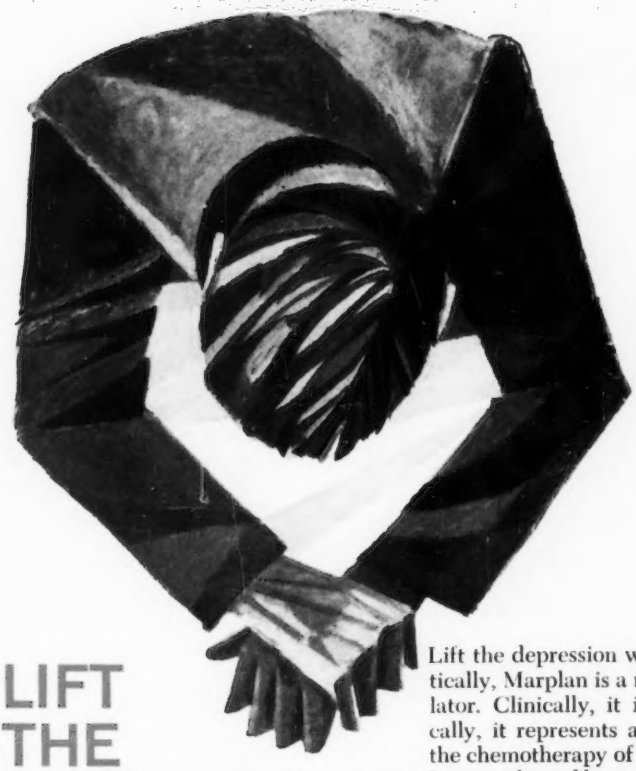
In the brief discussion of metastatic tumors the fanciful theory of Batson is dismissed summarily, and justly, as not in accord with the facts. However, the vertebral plexus of veins will doubtless continue to appear in textbooks for the next century.

In addition to the tumors of the central nervous system and its coverings, tumors of the nerve roots and of the peripheral ganglia and nerves are also discussed. The text ends with 37 pages by Prof. C. E. Lumsden on tissue culture in relation to tumors of the nervous system. Not only does it contain an account of his personal experience, much of it unpublished hitherto, but also the meager literature on the subject is critically evaluated. The bearing of the behavior of the tumor cells in culture upon the theories of the origin and nature of the neoplastic cells is discussed.

Since this reviewer is in fundamental accord with practically everything in this eminently reasonable and readable book, it is difficult to write at length about it. The text is clear and concise; the illustrations are well chosen and sharply reproduced. Although the book cannot compete in comprehensiveness with the treatises of Henschen or of Zülch, it is sufficiently complete to fulfill the hopes of the authors that "it will be of service not only to practising pathologists but to postgraduate students, neurologists and neurosurgeons." It is an excellent companion volume to Greenfield's "Neuropathology," and the pair fills a long-felt need for such a work in the English language.

Throughout the book the authors have not always remembered to distinguish between me and Orville, but this disturbs neither of us. The confusion between me and Pearce is even worse confounded, and this disturbs us even less; only his charming wife sometimes pretends to be annoyed when her flowers are delivered to my room in the hotel.

PERCIVAL BAILEY, M.D.



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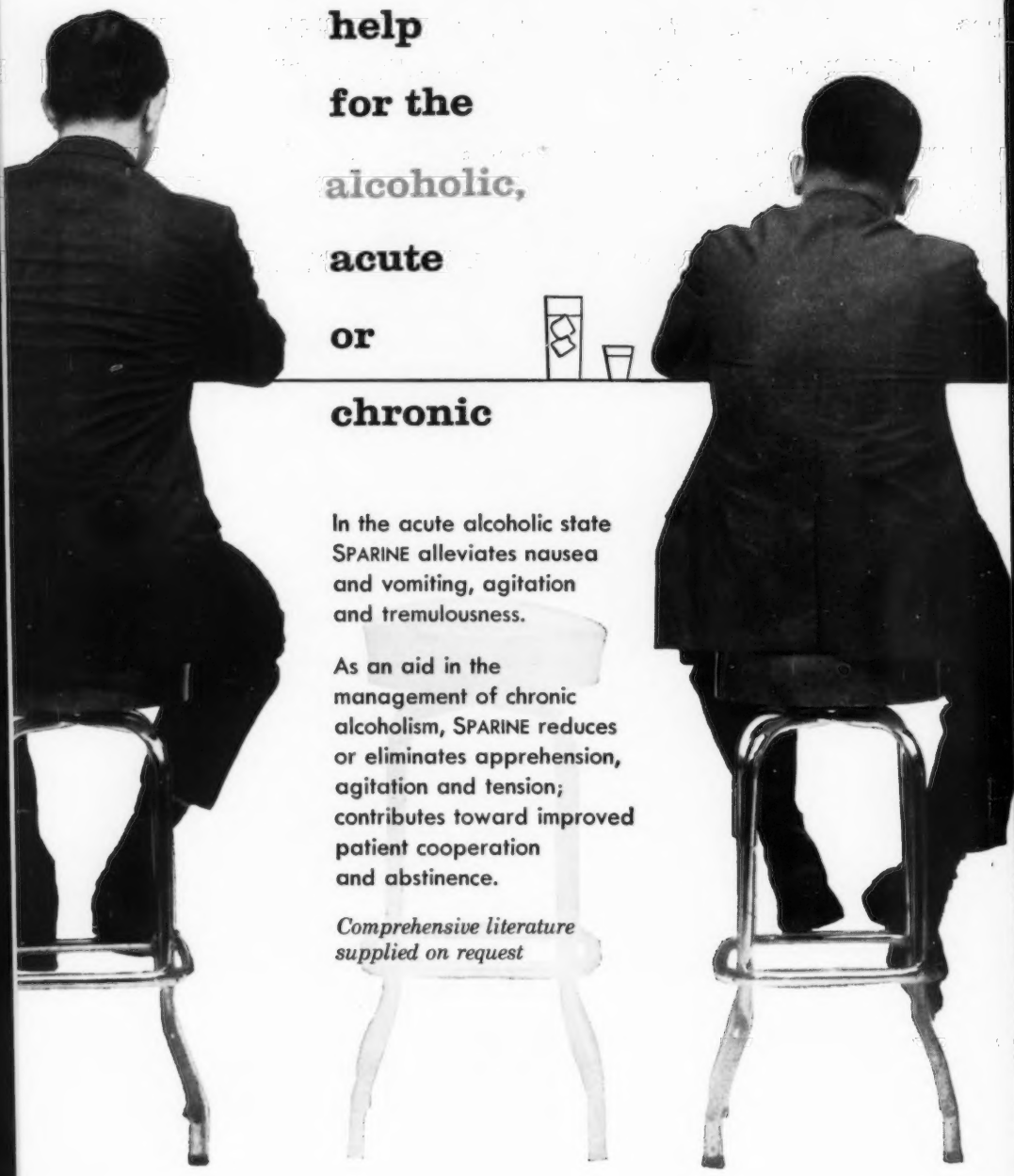

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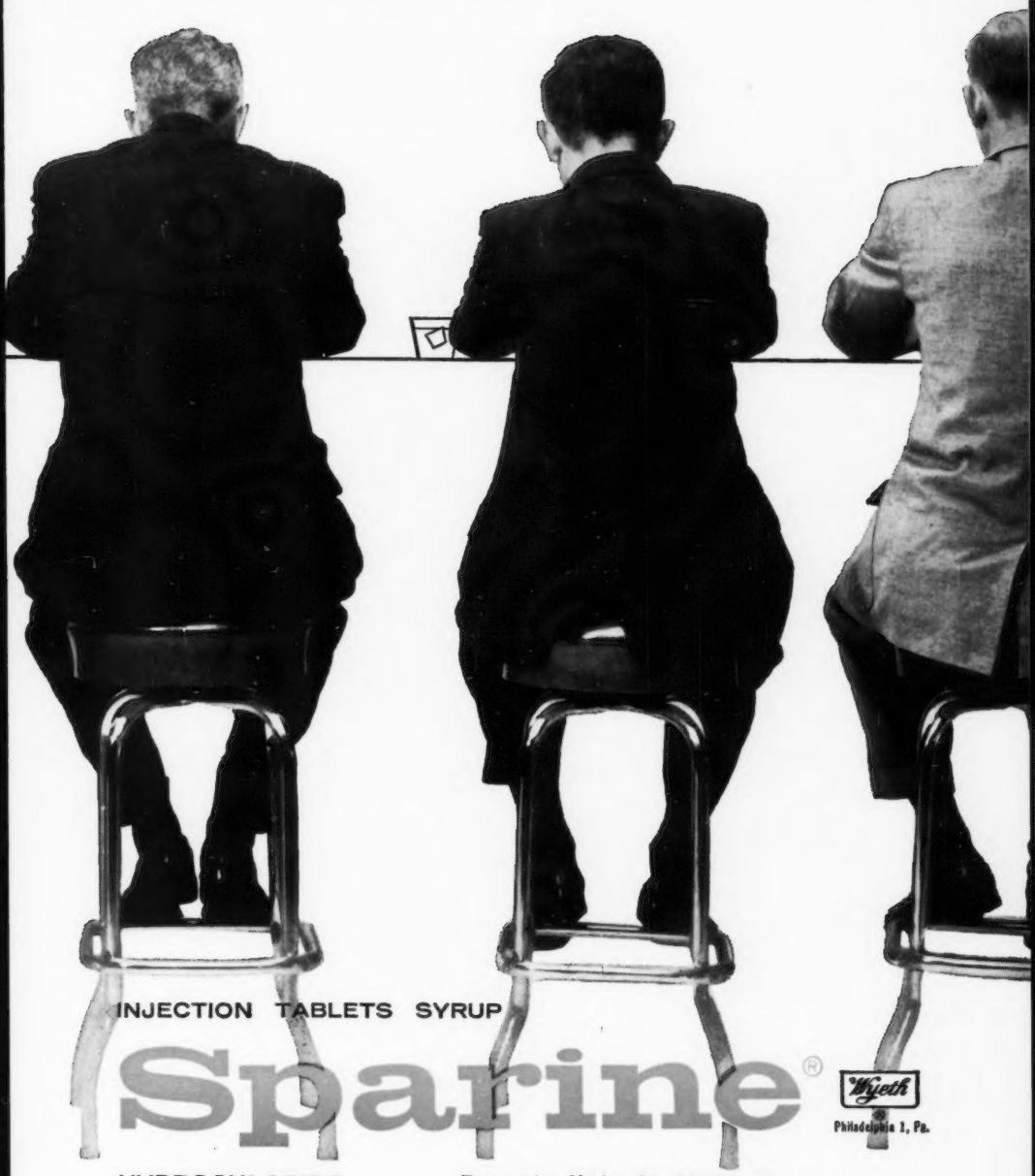

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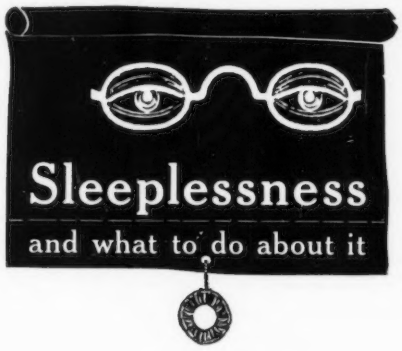

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Rudy, L.H.; Rinaldi, F.; Costa, E.; Himwich, H.E.; Tuteur, W., and Glotzer, J.: Trifluoperazine in the Treatment of Psychotic Patients, Am. J. Psychiat. *115*:364 (Oct.) 1958.

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Madgwick, J.R.A.; McNeill, D.L.M.; Driver, M., and Preston, G.C.: 'Stelazine' (Trifluoperazine), A Preliminary Report on a Clinical Trial, J. Ment. Sc. *104*:1195 (Dec.) 1958.

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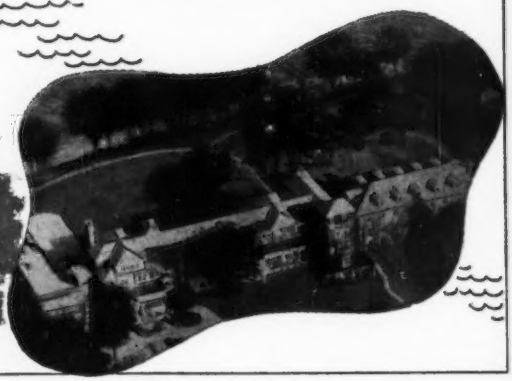

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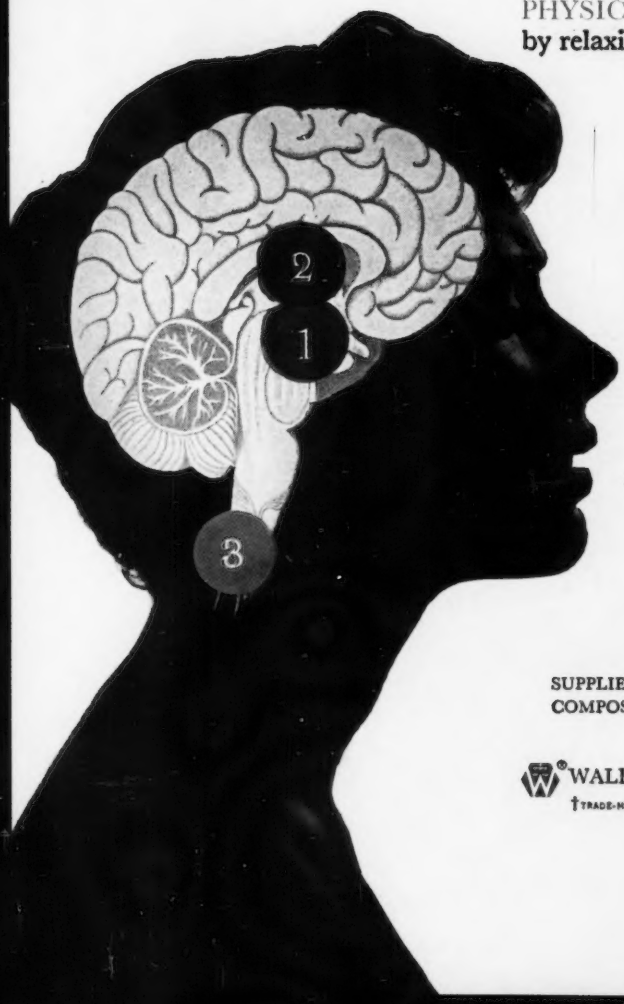

1
hypothalamus

2
thalamus and limbic system

3
spinal cord

▲Deprol▲†

benactyzine + meprobamate

- confirmed efficacy
- documented safety

SUPPLIED: Bottles of 50 light-pink, scored tablets
COMPOSITION: Each tablet contains 1 mg. benactyzine HCl and 400 mg. meprobamate

WALLACE LABORATORIES • *New Brunswick, N. J.*

†TRADE-MARK

CD-9289

remove
the
depression

with
new

Nardil

brand of phenelzine dihydrogen sulfate

a true antidepressant

Nardil

rapidly effective—antidepressant response often within a few days; complete remission usually within 2 to 6 weeks, in 4 out of 5 patients.[1-5]

low toxicity—no significant reports of toxicity to liver, blood or kidneys; side effects only occasional or mild in 3 years of exacting clinical trial and in thousands of cases to date.[1-4]

corrective—helps remove the depression, rather than merely masking the symptoms...this well tolerated yet potent monoamine oxidase inhibitor passes the blood-brain barrier rapidly with preferential distribution to the brain—not the liver ...restores the mild-to-deeply depressed or suicidal patient without institutionalization and without recourse to ECT in most cases.[1-4]

simple dosage schedule—1 tablet 3 times a day.

Indications: For the office or hospital treatment of mild to severe depressions, endogenous or reactive, and in depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis. Improves the depressed phase of affective (manic-depressive) psychosis, and relieves the depression of catatonic schizophrenics, although not affecting the psychosis *per se*.

Side Effects: Occasionally postural hypotension is seen, particularly in those patients whose pretreatment pressure is low. Infrequently reported nausea, ankle edema, delayed micturition or constipation is managed by appropriate adjunctive therapy, or will abate when dosage is reduced to maintenance level.

Dosage: One tablet three times a day. Maintain until remission of symptoms, which may require 2-6 weeks; then reduce to a maintenance level of 1 or 2 tablets a day. For the occasional patient who does not respond to the above starting dose, an additional one or two 15 mg. tablets may be given at bedtime.

Supplied: Orange-coated tablets, each containing 15 mg. of phenylethylhydrazine present as the dihydrogen sulfate. Bottles of 100.

Caution: Even though there have been no significant reports of toxic effects on the liver with the use of Nardil, as a matter of caution patients should be carefully followed with liver profile studies and the drug should be withheld or used with extreme care where the patient has a history of liver disease or where liver damage is present. Also, hypotensive patients should be under close medical supervision.

references: 1. Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. 2. Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. 3. Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* 116:71 (July) 1959. 4. Arnow, L. E.: Phenelzine: A Therapeutic Agent for Mental Depression, *Clinical Med.*, 6:1573 (Sept.) 1959. 5. Dickel, H. A.; Dixon, H. H.; Shanklin, J. G., and Dixon, H. H., Jr.: Tension Fatigue States and Their Adjunctive Treatment Using Nardil, *Clinical Med.*, 6:1579 (Sept.) 1959.

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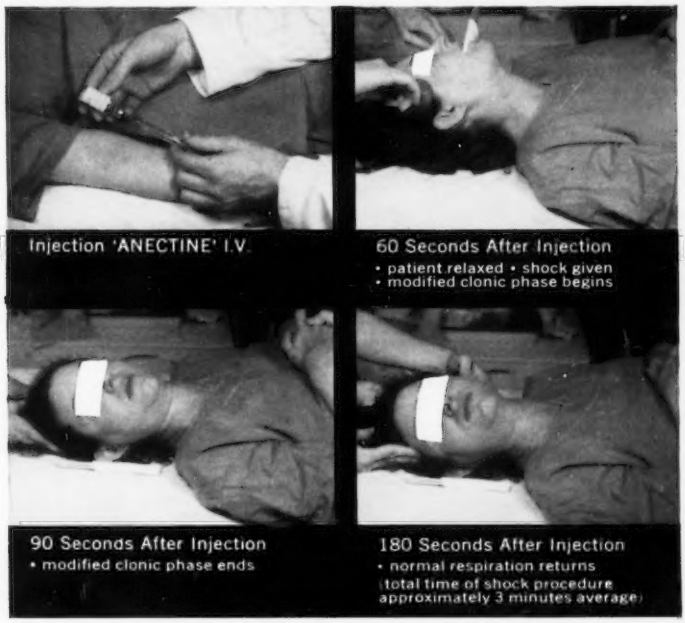
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• modified clonic phase begins
90 Seconds After Injection
• modified clonic phase ends
180 Seconds After Injection
• normal respiration returns
(total time of shock procedure approximately 3 minutes average)

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Comments from the literature:

"... method of choice."

Havens, L. L.: Dis. Nerv. System *19*:1 (Jan.) 1958.

"... recommend its use."

Impastato, D. J., and Gabriel, A. R.: Am. J. Psychiat. *114*:698 (Feb.) 1958.

"... treatment of choice."

Michael, K. D., and Wunderman, D. C.: J. Nerv. & Ment. Dis. *126*:535 (June) 1958.

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Robie, T. R.: J. M. Soc. New Jersey *52*:82 (Feb.) 1955.

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